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(54) Epígrafe: **DERIVADO DE QUINAZOLINA POSSUINDO ACTIVIDADE INIBIDORA DE TIROSINA-CINASE**

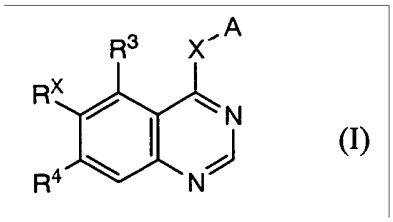
(57) Resumo:
É PROPORCIONADO UM COMPOSTO QUE INIBE A TIROSINA-CINASE RECEPTORA DE EGF E A TIROSINA-CINASE DE HER2. UM COMPOSTO REPRESENTADO PELA FÓRMULA GERAL (I): [FÓRMULA QUÍMICA 1] EM QUE RX É UM GRUPO REPRESENTADO PELA FÓRMULA: [FÓRMULA QUÍMICA 2] EM QUE R1 É UM ÁTOMO DE HIDROGÉNIO, ALQUILO OPCIONALMENTE SUBSTITUÍDO, ETC.; Z É -O-, -N(R10)-, ETC.; R10 É UM ÁTOMO DE HIDROGÉNIO, ALQUILO, ETC.; R2 É UM ÁTOMO DE HIDROGÉNIO, ALQUILO OPCIONALMENTE SUBSTITUÍDO, ETC.; R18 É UM ÁTOMO DE HIDROGÉNIO, ALQUILO OPCIONALMENTE SUBSTITUÍDO, ETC.; R19 É ALQUILO OPCIONALMENTE SUBSTITUÍDO, ETC.; W1 É UM GRUPO NÃO AROMÁTICO CONTENDO AZOTO OPCIONALMENTE SUBSTITUÍDO; R17 É UM ÁTOMO DE HIDROGÉNIO, ALQUILO OPCIONALMENTE SUBSTITUÍDO, ETC.; R3 E R4 SÃO INDEPENDENTEMENTE UM ÁTOMO DE HIDROGÉNIO, ALQUILO OPCIONALMENTE SUBSTITUÍDO, ETC.; X É -O-, -S- OU -N(R12)-, ETC.; R12 É UM ÁTOMO DE HIDROGÉNIO, ALQUILO, ETC.; E A É FENILO POSSUINDO OPCIONALMENTE UM SUBSTITUINTE, ETC., UM SEU SAL FARMACEUTICAMENTE ACEITÁVEL OU UM SEU SOLVATO.

RESUMO

"DERIVADO DE QUINAZOLINA POSSUINDO ACTIVIDADE INIBIDORA DE TIROSINA-CINASE"

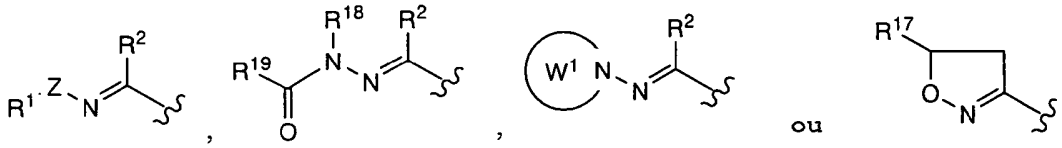
É proporcionado um composto que inibe a tirosina-cinase receptora de EGF e a tirosina-cinase de HER2. Um composto representado pela fórmula geral (I):

[Fórmula química 1]



em que R^x é um grupo representado pela fórmula:

[Fórmula química 2]



em que R^1 é um átomo de hidrogénio, alquilo opcionalmente substituído, etc.; Z é -O-, $-N(R^{10})-$, etc.; R^{10} é um átomo de hidrogénio, alquilo, etc.; R^2 é um átomo de hidrogénio, alquilo opcionalmente substituído, etc.; R^{18} é um átomo de hidrogénio, alquilo opcionalmente substituído, etc.; R^{19} é alquilo opcionalmente substituído, etc.; W^1 é um grupo não aromático

contendo azoto opcionalmente substituído; R^{17} é um átomo de hidrogénio, alquilo opcionalmente substituído, etc.; R^3 e R^4 são independentemente um átomo de hidrogénio, alquilo opcionalmente substituído, etc.; X é -O-, -S- ou -N(R^{12})-, etc.; R^{12} é um átomo de hidrogénio, alquilo, etc.; e A é fenilo possuindo opcionalmente um substituinte, etc.,

um seu sal farmaceuticamente aceitável ou um seu solvato.

DESCRIÇÃO

"DERIVADO DE QUINAZOLINA POSSUINDO ACTIVIDADE INIBIDORA DE TIROSINA-CINASE"

Campo técnico

A presente invenção refere-se a um composto que inibe a tirosina-cinase receptora de EGF e a tirosina-cinase de HER2, e a uma composição farmacêutica contendo-o como um ingrediente activo.

Técnica Anterior

A tirosina-cinase é uma enzima que fosforila resíduos de tirosina em proteínas substrato e é conhecida por desempenhar um papel importante num sistema de transdução de sinal intracelular relacionado com a diferenciação e proliferação celular. Duas tirosina-cinases receptoras, receptor de EGF (a seguir EGFR) e HER2 (também chamada ErbB2 ou Neu) estão consideravelmente envolvidas no desenvolvimento de cancro e as suas actividades estão aumentadas numa variedade de cancros humanos (Cancer Res., 1991, vol. 51, p. 4430-4435, Cancer Res., 1992, vol. 52, p. 3636-3641, Cancer Chemother. Pharmacol., 1993, vol. 32, p. 1-19). É também demonstrado que estas cinases são expressas de forma aberrante nos cancros do cérebro, pulmão, estômago, intestino, pâncreas, da parte da cabeça e pescoço, esófago, bexiga, rim, próstata, ovário, mama, útero e glândula tiróide (Expart. Opin. Invest. Drugs, 1994, vol. 3, nº 6, p. 577-595,

documento JP-5-208911). Por conseguinte, pensa-se que um inibidor destas cinases é útil como um fármaco anticancerígeno que pode ser eficaz em muitos tipos de cancros e tem poucos efeitos secundários. Os compostos descritos nos documentos WO92/20642, EP0520722, EP0566266, EP0602851, EP0520772, WO098/02434 são conhecidos como inibidores de tirosina-cinase.

Além disso, sabe-se que a transformação celular devido ao EGFR é acelerada pela coexpressão adicional de HER2 (Cell, 1989, vol. 58, p. 287-292). Além do mais, a expressão simultânea de EGFR e HER2 é referida como um marcador de mau prognóstico nos cancros da mama, cavidade oral e pulmão (Clin. Cancer Res., 1999, vol. 5, p. 4164-4174). Como um fármaco que inibe o EGFR e HER2 são conhecidos os compostos descritos na Literatura de Patentes 8.

Um agente anticancerígeno possuindo um substituinte tipo oxima na posição 4 de um derivado de quinazolina é descrito nos documentos WO2004/0691545 e WO2004/105765.

Divulgação da Invenção

Problemas a serem Resolvidos pela Invenção

Em comparação com um inibidor selectivo de EGFR ou HER2, prevê-se que um inibidor duplo de EGFR e HER2 seja mais eficaz, porque o último inibidor exibiria um efeito mais forte numa gama mais alargada de doenças devido ao efeito sinérgico de inibição dupla. Por conseguinte, tem sido desejado um composto que inibe os EGFR e HER2.

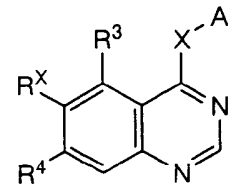
Meios para Resolver os Problemas

Na situação acima, a presente requerente estudou intensivamente e, como uma consequência, constatou que um derivado de quinazolina possuindo um determinado substituinte na posição 6 tem uma excelente actividade inibidora dupla no receptor de EGF e HER2.

Isto é, a presente invenção refere-se a:

(1) Um composto representado pela fórmula geral (I):

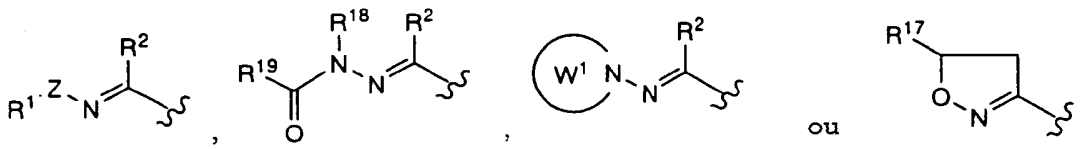
Fórmula química 1



(I)

em que R^x é um grupo representado pela fórmula:

Fórmula química 2



em que R^1 é um átomo de hidrogénio, alquilo opcionalmente substituído, alcenilo opcionalmente substituído, arilo opcionalmente substituído ou um grupo heterocíclico não aromático contendo azoto opcionalmente substituído;

Z é -O-, -N(R^{10})- ou alquileno, o qual pode estar intervalado com -O- ou -N(R^{11})-; em que R^{10} e R^{11} são independentemente um átomo de hidrogénio, alquilo, acilo, alquiloxicarbonilo, alceniloxicarbonilo ou aralquiloxicarbonilo;

R^2 é um átomo de hidrogénio, alquilo opcionalmente substituído, alcenilo opcionalmente substituído, alcinilo opcionalmente substituído, cicloalquilo opcionalmente substituído, arilo opcionalmente substituído ou heteroarilo opcionalmente substituído;

R^{19} é alquilo opcionalmente substituído, arilo opcionalmente substituído, heteroarilo opcionalmente substituído ou um grupo heterocíclico não aromático opcionalmente substituído;

R^{18} é um átomo de hidrogénio, alquilo opcionalmente substituído, alcenilo opcionalmente substituído ou alcinilo opcionalmente substituído;

W^1 é um grupo heterocíclico não aromático contendo azoto opcionalmente substituído ou heteroarilo opcionalmente substituído;

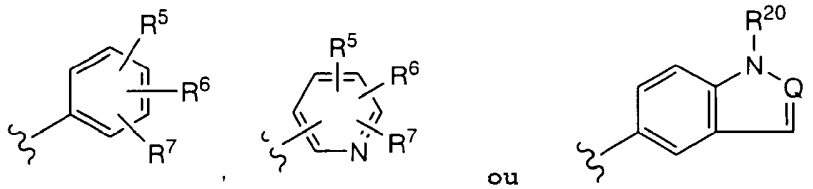
R^{17} é um átomo de hidrogénio, alquilo opcionalmente substituído, alcenilo opcionalmente substituído ou um grupo heterocíclico não aromático contendo azoto opcionalmente substituído;

R^3 e R^4 são independentemente um átomo de hidrogénio, alquilo opcionalmente substituído, alcenilo opcionalmente substituído, alcinilo opcionalmente substituído, alquiloxilo opcionalmente substituído, alceniloxilo opcionalmente substituído, halogéneo, hidroxilo, mercapto, ou amino opcionalmente substituído;

X é -O-, -S-, -N(R^{12})- ou alquileno, o qual pode estar intervalado com -O-, -S- ou -N(R^{13})-; em que R^{12} e R^{13} são independentemente um átomo de hidrogénio, alquilo, acilo, alquiloxicarbonilo, alceniloxicarbonilo ou aralquiloxicarbonilo; e

A é um grupo representado pela fórmula:

Fórmula química 3

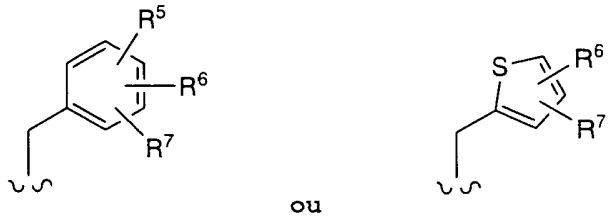


em que R^5 é um átomo de hidrogénio, halogéneo, alquiloxilo opcionalmente substituído, alceniloxilo opcionalmente substituído, alciniloxilo opcionalmente substituído ou um grupo representado pela fórmula: -Y-R^8 em que Y é -O-, -S-, -SO_2- ou alquileno, o qual pode estar intervalado com -O-, -S- ou -N(R^9)-, R^8 é arilo opcionalmente substituído ou heteroarilo opcionalmente substituído; R^9 é um átomo de hidrogénio, alquilo, acilo, alquiloxicarbonilo, alceniloxicarbonilo ou aralquiloxicarbonilo;

R^6 e R^7 são independentemente um átomo de hidrogénio, alquilo opcionalmente substituído, alcenilo opcionalmente substituído, alcinilo opcionalmente substituído, alquiloxilo opcionalmente substituído, alceniloxilo opcionalmente substituído, alciniloxilo opcionalmente substituído, halogéneo, hidroxilo, mercapto, ciano ou amino opcionalmente substituído;

R^{20} é alquilo opcionalmente substituído, alcenilo opcionalmente substituído, alcinilo opcionalmente substituído ou um grupo representado pela fórmula:

Fórmula química 4



em que R^5, R^6 e R^7 são como definidos acima;

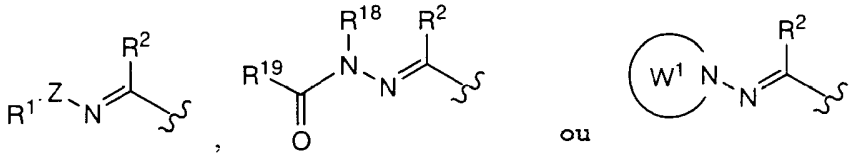
Q é N ou CH,

um seu sal farmaceuticamente aceitável ou um seu solvato.

Mais particularmente, a presente invenção refere-se aos (2) a (20) seguintes.

(2) O composto de acordo com (1), em que R^X é um grupo representado pela fórmula:

Fórmula química 5



em que R^1, R^2, R^{18}, R^{19}, Z e W^1 são como definidos em (1),

um seu sal farmaceuticamente aceitável ou um seu solvato.

(3) O composto de acordo com (1) ou (2), em que R^1 é alquilo opcionalmente substituído com um substituinte seleccionado do grupo substituinte A consistindo de hidroxilo, heteroarilo, carboxilo, amino opcionalmente substituído, grupo heterocíclico não aromático contendo azoto opcionalmente substituído, aminocarbonilo opcionalmente substituído e carbonilo heterocíclico não aromático contendo azoto opcionalmente substituído, ou um grupo heterocíclico não aromático contendo azoto opcionalmente substituído com um substituinte seleccionado do grupo substituinte B consistindo de alquiloxicarbonilo, aminocarbonilo opcionalmente substituído, oxo, amino, carboxilo, ciano, cianoalquilo, hidroxialquilo, alquilcarbonilamino, alquilsulfonilamino e aminocarbonilalquilo,

um seu sal farmaceuticamente aceitável ou um seu solvato.

(4) O composto de acordo com qualquer um de (1) a (3), em que R^1 é alquilo substituído com amino opcionalmente substituído com um substituinte seleccionado do grupo substituinte C consistindo de alquilo, alcenilo, alcinilo, arilo opcionalmente substituído, aralquilo, alquiloxilo, hidroxialquilo, hidroxialquiloxialquilo, haloalquilo, aminoalquilo opcionalmente substituído com 1 ou 2 alquilos, alquilsulfonilo, alquilsulfonilalquilo, alquilcarbonilo opcionalmente substituído com halogéneo ou alquiloxilo, alquiloxicarbonilo, cicloalquilo opcionalmente substituído, carboxialquilo, aminocarbonilalquilo opcionalmente substituído, aminocarboniloxialquilo opcionalmente substituído, alquiloxialquilo, alquiltioalquilo, alquilcarbonilaminoalquilo, alquilsulfonilaminoalquilo, alquilsulfonil(alquil)aminoalquilo, alquiloxicarbonilalquilo,

alquiltio(hidroxi)alquilo, cicloalquilalquilo, cianoalquilo, aminoalquilcarbonilo opcionalmente substituído, heteroarilo opcionalmente substituído, heteroarilalquilo, hidroxialquiloxialquilo, grupo heterocíclico não aromático opcionalmente substituído, e alquilo heterocíclico não aromático opcionalmente substituído, alquilo substituído com um grupo heterocíclico não aromático contendo azoto opcionalmente substituído com um substituinte seleccionado do grupo substituinte D consistindo de halogéneo; arilo; hidroxilo; oxo; aminocarbonilo opcionalmente substituído; alquiloxicarbonilo; alquilo opcionalmente substituído com um substituinte seleccionado do grupo substituinte H consistindo de aminocarbonilo opcionalmente substituído, ciano, alquiloxilo, alquilsulfonilamino, amino, carboxilo, alquiloxicarbonilo e hidroxilo; alquilaminocarbonilo; carboxilo; ciano; alquilsulfonilo; alquilcarbonilo; alcenilcarbonilo; alquilsulfonilalquilcarbonilo; alquiloxialquilcarbonilo; alquilcarbonilamino; aminocarboniloxilo; um grupo heterocíclico não aromático contendo azoto; e carbonilo heterocíclico não aromático ou um grupo heterocíclico não aromático contendo azoto opcionalmente substituído com um substituinte seleccionado do grupo substituinte B,

um seu sal farmaceuticamente aceitável ou um seu solvato.

(5) O composto de acordo com qualquer um de (1) a (4), em que Z é -O-, um seu sal farmaceuticamente aceitável ou um seu solvato.

(6) O composto de acordo com (1) ou (2), em que R^{19} é alquilo opcionalmente substituído com um substituinte seleccionado do grupo substituinte A; arilo opcionalmente

substituído com um substituinte seleccionado do grupo substituinte I consistindo de alquiloxicarbonilo, aminocarbonilo opcionalmente substituído, ciano, cianoalquilo, hidroxialquilo, e aminocarbonilalquilo, ou heteroarilo opcionalmente substituído com substituinte seleccionado do grupo substituinte I;

um seu sal farmaceuticamente aceitável ou um seu solvato.

(7) O composto de acordo com qualquer um de (1), (2) e (6), em que R^{19} é alquilo substituído com amino opcionalmente substituído com um substituinte seleccionado de um grupo substituinte C; ou

alquilo substituído com um grupo heterocíclico não aromático contendo azoto opcionalmente substituído com um substituinte seleccionado do grupo substituinte D;

um seu sal farmaceuticamente aceitável ou um seu solvato.

(8) O composto de acordo com (1) ou (2), em que W^1 é um grupo representado por um grupo heterocíclico não aromático contendo azoto opcionalmente substituído com um substituinte seleccionado do grupo substituinte J consistindo de alquilo, cianoalquilo, hidroxialquilo, aminocarbonilalquilo, alquiloxilo, alquiloxicarbonilo, aminocarbonilo opcionalmente substituído, e ciano; ou

um grupo representado por heteroarilo opcionalmente substituído com um substituinte seleccionado do grupo substituinte J;

um seu sal farmaceuticamente aceitável ou um seu solvato.

(9) O composto de acordo com qualquer um de (1) a (8), em que R^2 é um átomo de hidrogénio, alquilo C1-C6 opcionalmente substituído com halogéneo, alcenilo C2-C6, alcinilo C2-C6, halogéneo ou fenilo,

um seu sal farmaceuticamente aceitável ou um seu solvato.

(10) O composto de acordo com qualquer um de (1) a (9), em que R^2 é alcinilo C2-C4,

um seu sal farmaceuticamente aceitável ou um seu solvato.

(11) O composto de acordo com qualquer um de (1) a (10), em que um de R^3 e R^4 é um átomo de hidrogénio, e o outro é um átomo de hidrogénio, alquiloxilo opcionalmente substituído ou alceniloxilo opcionalmente substituído,

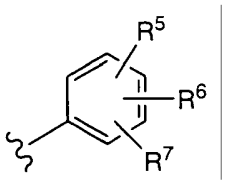
um seu sal farmaceuticamente aceitável ou um seu solvato.

(12) O composto de acordo com qualquer um de (1) a (11), em que X é -NH-,

um seu sal farmaceuticamente aceitável ou um seu solvato.

(13) O composto de acordo com qualquer um de (1) a (12), em que A é um grupo representado pela fórmula:

Fórmula química 6

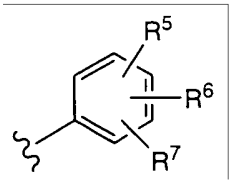


em que R^5 é um átomo de hidrogénio ou halogéneo; R^6 é halogéneo ou alcinilo; e R^7 é um átomo de hidrogénio,

um seu sal farmaceuticamente aceitável ou um seu solvato.

(14) O composto de acordo com qualquer um de (1) a (12), em que A é um grupo representado pela fórmula:

Fórmula química 7



em que R^5 é alquiloxilo opcionalmente substituído com um substituinte seleccionado do grupo substituinte E consistindo de carboxilo, alcoxioxicarbonilo, cicloalquilo e aminocarbonilo opcionalmente substituído;

alceniloxilo opcionalmente substituído com um substituinte seleccionado do grupo substituinte E; ou

alciniloxilo opcionalmente substituído com um substituinte seleccionado do grupo substituinte E;

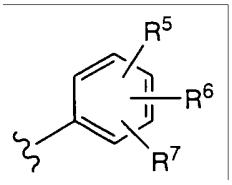
R^6 está alcinilo opcionalmente substituído, alquiloxilo opcionalmente substituído ou halogéneo; e

R^7 é um átomo de hidrogénio,

um seu sal farmaceuticamente aceitável ou um seu solvato.

(15) O composto de acordo com qualquer um de (1) a (12), em que A é um grupo representado pela fórmula:

Fórmula química 8



em que R^5 é um grupo representado pela fórmula: $-Y-R^8$ em que Y é alquileno, o qual pode estar intervalado com -O-;

R^8 é fenilo opcionalmente substituído com substituinte seleccionado de um grupo substituinte F consistindo de halogéneo, carboxilo, alquilo, haloalquilo, hidroxialquilo, alquiloxilo, alquiloxicarbonilo e amino opcionalmente substituído;

piridilo opcionalmente substituído com um substituinte seleccionado do grupo substituinte F;

furilo opcionalmente substituído com um substituinte seleccionado do grupo substituinte F;

tienilo opcionalmente substituído com um substituinte seleccionado do grupo substituinte F;

tiazolilo opcionalmente substituído com um substituinte seleccionado do grupo substituinte F; ou

oxazolilo opcionalmente substituído com um substituinte seleccionado do grupo substituinte F;

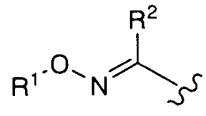
R^6 está alcinilo opcionalmente substituído, alquiloxilo opcionalmente substituído ou halogéneo; e

R^7 é um átomo de hidrogénio,

um seu sal farmaceuticamente aceitável ou um seu solvato.

(16) O composto de acordo com (1), em que R^X é um grupo representado pela fórmula:

Fórmula química 9



em que R^1 é alquilo substituído com amino opcionalmente substituído com alquilo, hidroxialquilo, alquilcarbonilaminoalquilo ou um heterociclo não aromático;

alquilo substituído com um heterociclo não aromático contendo azoto opcionalmente substituído com alquilo, hidroxialquilo ou alquilcarbonilamino; ou

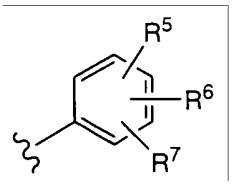
um grupo heterocíclico não aromático contendo azoto substituído com hidroxialquilo; e R^2 é alcinilo C2-C4;

R^3 e R^4 são ambos um átomo de hidrogénio;

X é -NH-; e

A é um grupo representado pela fórmula:

Fórmula química 10



em que R^5 é um grupo representado pela fórmula: -Y-R^8 em que Y é alquileno C1-C3, o qual pode estar intervalado com -O-;

R^8 é fenilo opcionalmente substituído com halogéneo, ou piridilo opcionalmente substituído com halogéneo;

R^6 é halogéneo; e

R^7 é um átomo de hidrogénio,

um seu sal farmaceuticamente aceitável ou um seu solvato.

(17) Uma composição farmacêutica contendo o composto como definido em qualquer um de (1) a (16) como um ingrediente activo.

(18) Uma composição farmacêutica útil para o tratamento de cancro contendo o composto como definido em qualquer um de (1) a (16) como um ingrediente activo.

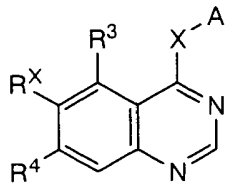
(19) Um método para prevenir e/ou tratar um cancro, compreendendo administrar o composto de acordo com qualquer um de (1) a (16), um seu sal farmaceuticamente aceitável ou um seu solvato.

(20) Utilização do composto de acordo com qualquer um de (1) a (16), seu solvato farmaceuticamente aceitável ou um sal para produzir uma composição para prevenir e/ou tratar um cancro.

Além disso, a presente invenção inclui as seguintes invenções como outro aspecto.

(I) Um composto representado pela fórmula geral (I):

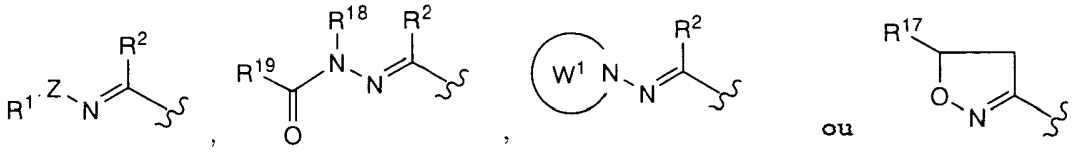
Fórmula química 11



(I)

em que R^X é um grupo representado pela fórmula:

Fórmula química 12



em que R^1 é um átomo de hidrogénio, alquilo opcionalmente substituído, alcenilo opcionalmente substituído ou um grupo heterocíclico não aromático contendo azoto opcionalmente substituído;

Z é -O- ou -N(R^{10})- ou alquileno, o qual pode estar intervalado com -O- ou -N(R^{11})-; R^{10} e R^{11} são independentemente um átomo de hidrogénio, alquilo, acilo, alquiloxicarbonilo, alceniloxicarbonilo ou aralquiloxicarbonilo;

R^2 é um átomo de hidrogénio, alquilo opcionalmente substituído, alcenilo opcionalmente substituído, alcinilo opcionalmente substituído, arilo opcionalmente substituído ou heteroarilo opcionalmente substituído;

R^{19} é alquilo opcionalmente substituído, arilo opcionalmente substituído, heteroarilo opcionalmente substituído ou um grupo heterocíclico não aromático opcionalmente substituído;

R^{18} é um átomo de hidrogénio, alquilo opcionalmente substituído, alcenilo opcionalmente substituído ou alcinilo opcionalmente substituído;

W^1 é um grupo heterocíclico não aromático contendo azoto opcionalmente substituído ou heteroarilo opcionalmente substituído;

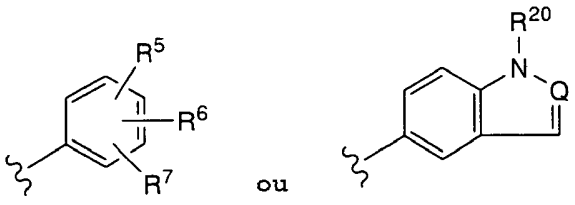
R^{17} é um grupo hidrogénio, alquilo opcionalmente substituído, alcenilo opcionalmente substituído ou grupo heterocíclico não aromático contendo azoto opcionalmente substituído;

R^3 e R^4 são independentemente um átomo de hidrogénio, alquilo opcionalmente substituído, alcenilo opcionalmente substituído, alcinilo opcionalmente substituído, alquiloxilo opcionalmente substituído, alceniloxilo opcionalmente substituído, halogéneo, hidroxilo, mercapto ou amino opcionalmente substituído;

X é -O-, -S-, $-N(R^{12})-$ ou alquileno, o qual pode estar intervalado com -O-, -S- ou $-N(R^{13})-$; em que R^{12} e R^{13} são independentemente um átomo de hidrogénio, alquilo, acilo, alquiloxicarbonilo, alceniloxicarbonilo ou aralquiloxicarbonilo; e

A é um grupo representado pela fórmula:

Fórmula química 13



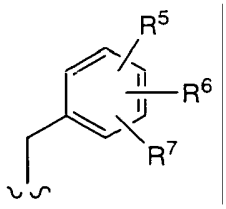
em que R^5 é um átomo de hidrogénio, halogéneo, alquiloxilo opcionalmente substituído, alceniloxilo opcionalmente

substituído, alciniloxilo opcionalmente substituído ou um grupo representado pela fórmula: $-Y-R^8$ em que Y é -O-, -S- ou alquileno, o qual pode estar intervalado com $-N(R^9)-$; R^8 é arilo opcionalmente substituído ou heteroarilo opcionalmente substituído; R^9 é um átomo de hidrogénio, alquilo, acilo, alquiloxicarbonilo, alceniloxicarbonilo ou aralquiloxicarbonilo;

R^6 e R^7 são independentemente um átomo de hidrogénio, alquilo opcionalmente substituído, alcenilo opcionalmente substituído, alcinilo opcionalmente substituído, alquiloxilo opcionalmente substituído, alceniloxilo opcionalmente substituído, alciniloxilo opcionalmente substituído, halogéneo, hidroxilo, mercapto ou amino opcionalmente substituído;

R^{20} é alquilo opcionalmente substituído, alcenilo opcionalmente substituído, alcinilo opcionalmente substituído ou um grupo representado pela fórmula:

Fórmula química 14



em que R^5, R^6 e R^7 são como definidos acima;

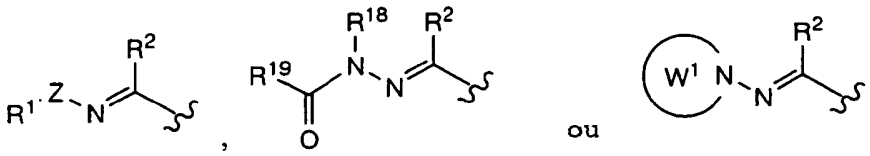
Q é N ou CH_2,

um seu sal farmaceuticamente aceitável ou um seu solvato.

Mais particularmente, a presente invenção refere-se às (II) a (XV) seguintes.

(II) Um composto de acordo com (I), em que R^X é um grupo representado pela fórmula:

Fórmula química 15



em que R^1, R^2, R^{18}, R^{19}, Z e W^1 são como definidos em (I),

um seu sal farmaceuticamente aceitável ou um seu solvato.

(III) O composto de acordo com (I) ou (II), em que R^1 é alquilo opcionalmente substituído com um substituinte seleccionado do grupo substituinte A' consistindo de hidroxilo, amino opcionalmente substituído, grupo heterocíclico não aromático contendo azoto opcionalmente substituído, aminocarbonilo opcionalmente substituído e carbonilo heterocíclico não aromático contendo azoto opcionalmente substituído, ou

um grupo heterocíclico não aromático contendo azoto opcionalmente substituído com um substituinte seleccionado do grupo substituinte B' consistindo de alquiloxicarbonilo, aminocarbonilo opcionalmente substituído, ciano, cianoalquilo, hidroxialquilo e aminocarbonilalquilo,

um seu sal farmaceuticamente aceitável ou um seu solvato.

(IV) O composto de acordo com qualquer um de (I) a (III), em que R^1 é alquilo opcionalmente substituído com amino substituído com um substituinte seleccionado do grupo substituinte C' consistindo de alquilo, alcinilo, alquilsulfonilalquilo, hidroxialquilo, alquilcarbonilo opcionalmente substituído com halogéneo, alquiloxicarbonilo, cicloalquilo, opcionalmente substituído com aminocarbonilalquilo, aminocarboniloxialquilo opcionalmente substituído, alquiloxialquilo, cicloalquilalquilo, cianoalquilo e aminoalquilcarbonilo opcionalmente substituído, ou

alquilo substituído com um grupo heterocíclico não aromático contendo azoto opcionalmente substituído com um substituinte seleccionado de um grupo substituinte D' consistindo de hidroxilo; oxo; aminocarbonilo opcionalmente substituído; alquiloxicarbonilo; alquilo opcionalmente substituído com um substituinte seleccionado do grupo substituinte H' consistindo de aminocarbonilo opcionalmente substituído, ciano, alquiloxilo, e hidroxilo; alquilaminocarbonilo; ciano; alquilsulfonilo; alquilcarbonilo; alcenilcarbonilo; alquilsulfonilalquilcarbonilo; alquiloxialquilcarbonilo; alquilcarbonilamino; e carbonilo heterocíclico não aromático,

um seu sal farmaceuticamente aceitável ou um seu solvato.

(V) O composto de acordo com (I) ou (II), em que R^{19} é alquilo opcionalmente substituído com um substituinte seleccionado do grupo substituinte A', arilo opcionalmente substituído com um substituinte seleccionado do grupo substituinte I' consistindo de alquiloxicarbonilo,

aminocarbonilo opcionalmente substituído, ciano, cianoalquilo, hidroxialquilo e aminocarbonilalquilo, ou heteroarilo substituído com um substituinte seleccionado do grupo substituinte I',

um seu sal farmaceuticamente aceitável ou um seu solvato.

(VI) O composto de acordo com qualquer um de (I), (II) e (V), em que R^{19} é alquilo substituído com amino opcionalmente substituído com um substituinte seleccionado do grupo substituinte C', ou

alquilo substituído com um grupo heterocíclico não aromático contendo azoto opcionalmente substituído com um substituinte seleccionado do grupo substituinte D',

um seu sal farmaceuticamente aceitável ou um seu solvato.

(VII) O composto de acordo com (I) ou (II), em que W^1 é um grupo representado por um grupo heterocíclico não aromático contendo azoto opcionalmente substituído com um substituinte seleccionado do grupo substituinte J' consistindo de alquilo, cianoalquilo, hidroxialquilo, aminocarbonilalquilo, alquiloxilo, alquiloxicarbonilo, aminocarbonilo opcionalmente substituído e ciano, ou

um grupo representado por heteroarilo opcionalmente substituído com um substituinte seleccionado do grupo substituinte J',

um seu sal farmaceuticamente aceitável ou um seu solvato.

(VIII) O composto de acordo com qualquer um de (I) a (VII), em que R^2 é um átomo de hidrogénio, alquilo C1-C6 opcionalmente substituído com halogéneo, alcenilo C2-C6, alcinilo C2-C6, halogéneo ou fenilo,

um seu sal farmaceuticamente aceitável ou um seu solvato.

(IX) O composto de acordo com qualquer um de (I) a (VIII), em que um de R^3 e R^4 é um átomo de hidrogénio, e o outro é um átomo de hidrogénio, alquiloxilo opcionalmente substituído ou alceniloxilo opcionalmente substituído,

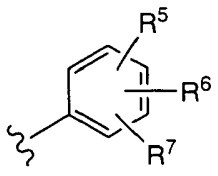
um seu sal farmaceuticamente aceitável ou um seu solvato.

(X) O composto de acordo com qualquer um de (I) a (IX), em que X é -NH-,

um seu sal farmaceuticamente aceitável ou um seu solvato.

(XI) O composto de acordo com qualquer um de (I) a (IX), em que A é um grupo representado pela fórmula:

Fórmula química 16

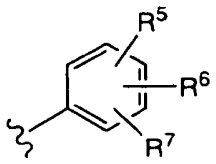


em que R^5 é um átomo de hidrogénio ou halogéneo; R^6 é halogéneo ou alcinilo; e R^7 é um hidrogénio,

um seu sal farmaceuticamente aceitável ou um seu solvato.

(XII) O composto de acordo com qualquer um de (I) a (IX), em que A é um grupo representado pela fórmula:

Fórmula química 17



em que R^5 é alquiloxilo opcionalmente substituído com um substituinte seleccionado do grupo substituinte E' consistindo de carboxilo, alquiloxicarbonilo, cicloalquilo e aminocarbonilo opcionalmente substituído,

alceniloxilo opcionalmente substituído com um substituinte seleccionado do grupo substituinte E', ou

alciniloxilo opcionalmente substituído com um substituinte seleccionado do grupo substituinte E';

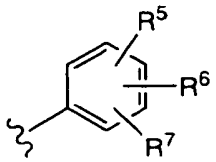
R^6 é alcinilo opcionalmente substituído, alquiloxilo opcionalmente substituído ou halogéneo; e

R^7 é um átomo de hidrogénio,

um seu sal farmaceuticamente aceitável ou um seu solvato.

(XIII) O composto de acordo com qualquer um de (I) a (IX), em que A é um grupo representado pela fórmula:

Fórmula química 18



em que R^5 é um grupo representado pela fórmula: $-Y-R^8$ em que Y é alquileno, o qual pode estar intervalado com -O-;

R^8 é fenilo opcionalmente substituído com um substituinte seleccionado do grupo substituinte F' consistindo de halogéneo, carboxilo, alquilo, haloalquilo, hidroxialquilo, alquiloxilo, alquiloxicarbonilo, e amino opcionalmente substituído;

piridilo opcionalmente substituído com um substituinte seleccionado do grupo substituinte F';

furilo opcionalmente substituído com um substituinte seleccionado de um grupo substituinte F';

tienilo opcionalmente substituído com um substituinte seleccionado de um grupo substituinte F';

tiazolilo opcionalmente substituído com um substituinte seleccionado de um grupo substituinte F'; ou

oxazolilo opcionalmente substituído com um substituinte seleccionado de um grupo substituinte F';

R^6 é alcinilo opcionalmente substituído, alquiloxilo opcionalmente substituído ou halogéneo; e
R^7 é um átomo de hidrogénio,

um seu sal farmaceuticamente aceitável ou um seu solvato.

(XIV) Uma composição farmacêutica contendo o composto como definido em qualquer um de (I) a (XIII) como um ingrediente activo.

(XV) Uma composição farmacêutica útil para o tratamento de cancro contendo o composto como definido em qualquer um de (I) a (XIII) como um ingrediente activo.

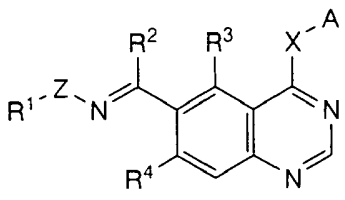
(XVI) Um método para prevenir e/ou tratar um cancro, compreendendo administrar o composto como definido em qualquer um de (I) a (XIII), um seu sal farmaceuticamente aceitável ou um seu solvato.

(XVII) Utilização do composto como definido em qualquer um de (I) a (XIII), um seu sal farmaceuticamente aceitável ou um seu solvato para produzir uma composição para prevenir e/ou um cancro.

Ainda um outro aspecto da presente invenção inclui as seguintes invenções.

(i) Um composto representado pela fórmula geral (I'):

Fórmula química 19



(I')

em que R^1 é um átomo de hidrogénio, alquilo opcionalmente substituído, alcenilo opcionalmente substituído ou grupo heterocíclico não aromático contendo azoto opcionalmente substituído;

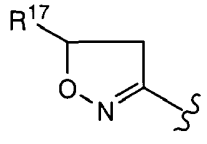
Z é -O- ou -N(R^{10})- ou alquileno, o qual pode estar intervalado com -O- ou -N(R^{11})-;

R^{10} e R^{11} são independentemente um átomo de hidrogénio, alquilo, acilo, alquiloxicarbonilo, alceniloxicarbonilo ou aralquiloxicarbonilo;

R^2 é um átomo de hidrogénio, alquilo opcionalmente substituído, alcenilo, alcinilo, arilo opcionalmente substituído ou heteroarilo opcionalmente substituído ou

um grupo representado por -C(R^2)= N-Z-R^1 é um grupo representado pela fórmula:

Fórmula química 20



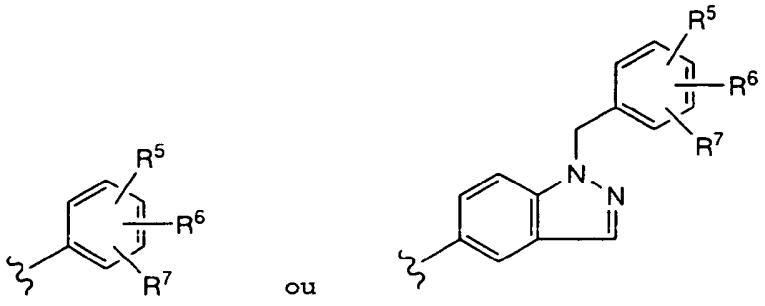
em que R^{17} é um átomo de hidrogénio, alquilo opcionalmente substituído, alcenilo opcionalmente substituído ou um grupo heterocíclico não aromático contendo azoto opcionalmente substituído;

R^3 e R^4 são independentemente um átomo de hidrogénio, alquilo opcionalmente substituído, alcenilo opcionalmente substituído, alcinilo opcionalmente substituído, alquiloxilo opcionalmente substituído, alceniloxilo opcionalmente substituído, halogéneo, hidroxilo, mercapto ou amino opcionalmente substituído;

X é -O-, -S- ou $-N(R^{12})-$ ou alquileno, o qual pode estar intervalado com -O-, -S- ou $-N(R^{13})-$; em que R^{12} e R^{13} são independentemente um átomo de hidrogénio, alquilo, acilo, alquiloxicarbonilo, alceniloxicarbonilo ou aralquiloxicarbonilo; e

A é um grupo representado pela fórmula:

Fórmula química 21



em que R^5 é um átomo de hidrogénio, halogéneo, alquiloxilo opcionalmente substituído, alceniloxilo opcionalmente substituído, alciniloxilo opcionalmente substituído ou um grupo

representado pela fórmula: $-Y-R^8$ em que Y é -O-, -S- ou alquileno, o qual pode estar intervalado com $-N(R^9)-$; R^8 é arilo opcionalmente substituído ou heteroarilo opcionalmente substituído; R^9 é um átomo de hidrogénio, alquilo, acilo, alquiloxicarbonilo, alceniloxicarbonilo ou aralquiloxicarbonilo;

R^6 e R^7 são independentemente um átomo de hidrogénio, alquilo opcionalmente substituído, alcenilo opcionalmente substituído, alcinilo opcionalmente substituído, alquiloxilo opcionalmente substituído, alceniloxilo opcionalmente substituído, alciniloxilo opcionalmente substituído, halogéneo, hidroxilo, mercapto ou amino opcionalmente substituído,

um seu sal farmaceuticamente aceitável ou um seu solvato.

(ii) O composto de acordo com (i), em que R^1 é alquilo opcionalmente substituído com um substituinte seleccionado do grupo substituinte A" consistindo de amino opcionalmente substituído e grupo heterocíclico não aromático contendo azoto opcionalmente substituído, ou

um grupo heterocíclico não aromático contendo azoto opcionalmente substituído com um substituinte seleccionado do grupo substituinte B" consistindo de alquiloxicarbonilo, aminocarbonilo opcionalmente substituído, e ciano,

um seu sal farmaceuticamente aceitável ou um seu solvato.

(iii) O composto de acordo com (i) ou (ii), em que R^1 é alquilo substituído com amino opcionalmente substituído com um substituinte seleccionado do grupo substituinte C" consistindo de alquilo, alquilsulfonilalquilo, alquilcarbonilo opcionalmente

substituído com halogéneo, alquiloxicarbonilo, cicloalquilo, aminocarbonilalquilo opcionalmente substituído, aminocarboniloxialquilo opcionalmente substituído, alquiloxialquilo e aminoalquilcarbonilo opcionalmente substituído, ou

alquilo substituído com um grupo heterocíclico não aromático contendo azoto opcionalmente substituído com um substituinte seleccionado do grupo substituinte D" consistindo de oxo, aminocarbonilo opcionalmente substituído, alquiloxicarbonilo, alquilo opcionalmente substituído com ciano ou alquiloxilo, ciano, alquilsulfonilo, alquilcarbonilo, alcenilcarbonilo e alquilsulfonilalquilcarbonilo,

um seu sal farmaceuticamente aceitável ou um seu solvato.

(iv) O composto de acordo com qualquer um de (i) a (iii), em que um de R^3 e R^4 é um átomo de hidrogénio, e o outro é um átomo de hidrogénio, alquiloxilo opcionalmente substituído ou alceniloxilo opcionalmente substituído,

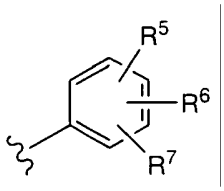
um seu sal farmaceuticamente aceitável ou um seu solvato.

(v) O composto de acordo com qualquer um de (i) a (iv), em que X é -NH-,

um seu sal farmaceuticamente aceitável ou um seu solvato.

(vi) O composto de acordo com qualquer um de (i) a (v), em que A é um grupo representado pela fórmula:

Fórmula química 22

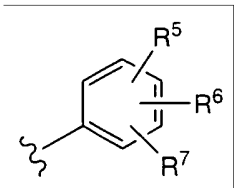


em que R^5 é um átomo de hidrogénio ou halogéneo; R^6 é halogéneo ou alcinilo; e R^7 é um átomo de hidrogénio,

um seu sal farmaceuticamente aceitável ou um seu solvato.

(vii) O composto de acordo com qualquer um de (i) a (vi), em que A é um grupo representado pela fórmula:

Fórmula química 23



em que R^5 é alquiloxilo opcionalmente substituído com um substituinte seleccionado do grupo substituinte E" consistindo de carboxilo, alquiloxicarbonilo e aminocarbonilo opcionalmente substituído,

alceniloxilo opcionalmente substituído com um substituinte seleccionado de um grupo substituinte E", ou

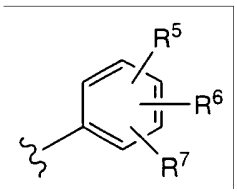
alciniloxilo opcionalmente substituído com um substituinte seleccionado de um grupo substituinte E";

R^6 é alcinilo opcionalmente substituído, alquiloxilo opcionalmente substituído ou halogéneo; e

R^7 é um átomo de hidrogénio, um seu sal farmaceuticamente aceitável ou um seu solvato.

(viii) O composto de acordo com qualquer um de (i) a (vii), em que A é um grupo representado pela fórmula:

Fórmula química 24



em que R^5 é um grupo representado pela fórmula: $-Y-R^8$ em que Y é alquileno, o qual pode estar intervalado com -O-;

R^8 é fenilo opcionalmente substituído com um substituinte seleccionado do grupo substituinte F" consistindo de halogéneo, carboxilo, alquilo, haloalquilo, hidroxialquilo, alquiloxilo, alquiloxicarbonilo e amino opcionalmente substituído;

piridilo opcionalmente substituído com um substituinte seleccionado de um grupo substituinte F";

furilo opcionalmente substituído com um substituinte seleccionado de um grupo substituinte F";

tienilo opcionalmente substituído com um substituinte seleccionado de um grupo substituinte F";

tiazolilo opcionalmente substituído com um substituinte seleccionado de um grupo substituinte F"; ou

oxazolilo opcionalmente substituído com um substituinte seleccionado de um grupo substituinte F";

R^6 é alcinilo opcionalmente substituído, alquiloxilo opcionalmente substituído ou halogéneo; e

R' é um átomo de hidrogénio,

um seu sal farmaceuticamente aceitável ou um seu solvato.

(ix) Uma composição farmacêutica contendo o composto como definido em qualquer um de (i) a (viii) como um ingrediente activo.

(x) Uma composição farmacêutica útil para o tratamento de cancro contendo o composto como definido em qualquer um de (i) a (viii) como um ingrediente activo.

(xi) Um método para prevenir e/ou tratar um cancro, compreendendo administrar o composto como definido em qualquer um de (i) a (viii), um seu sal farmaceuticamente aceitável ou um seu solvato.

(xii) Utilização do composto como definido em qualquer um de (i) a (viii), um seu sal farmaceuticamente aceitável ou um seu solvato para produzir uma composição para prevenir e/ou tratar um cancro.

Como aqui utilizado, o "halogéneo" significa flúor, cloro, bromo ou iodo. O flúor, cloro e bromo são preferidos.

Como aqui utilizado, o "alquilo", o qual é utilizado sozinho ou em associação com outro termo, inclui um grupo hidrocarboneto monovalente linear ou ramificado possuindo 1 a 10 átomo(s) de carbono. Os exemplos incluem metilo, etilo, n-propilo, isopropilo, n-butilo, isobutilo, sec-butilo, terc-butilo, n-pentilo, isopentilo, neo-pentilo, n-hexilo, iso-hexilo, n-heptilo, n-octilo, n-nonanilo e n-decanilo. Os exemplos preferidos incluem alquilo C1-C10. Os exemplos mais preferidos incluem alquilo C1-C6. Os exemplos muito preferidos incluem alquilo C1-C4.

Como aqui utilizado, o termo "haloalquilo", o qual é utilizado sozinho ou em associação com outro termo, inclui o "alquilo" que está substituído com o "halogéneo" em 1 a 8 sítios, de um modo preferido 1 a 5 sítios. Os exemplos incluem trifluorometilo, triclorometilo, difluoroetilo, trifluoroetilo, dicloroetilo e tricloroetilo. Os exemplos preferidos incluem alquilo C1-C6 que está substituído com o "halogéneo" em 1 a 5 sítios. Em particular, é preferido o alquilo C1-C3 substituído com o "halogéneo" em 1 a 3 sítios. Os exemplos muito preferidos incluem trifluorometilo.

Como aqui utilizado, o "alquilsulfonilo" inclui metilsulfonilo, etilsulfonilo e propilsulfonilo. Os exemplos

preferidos incluem alquilsulfonilo C1-C6. Em particular, é preferido o alquilsulfonilo C1-C3.

Como aqui utilizado, os exemplos do "alquilsulfonilalquilo" incluem metilsulfonilmetilo, metilsulfoniletilo, metilsulfonilpropilo, metilsulfonilbutilo e metilsulfonilpropilo. Os exemplos preferidos incluem alquilsulfonil C1-C6-alquilo C1-C6. Em particular, é preferido o alquilsulfonil C1-C3-alquilo C1-C4.

Como aqui utilizado, os exemplos do "alquiloxilo" incluem metiloxilo, etiloxilo, n-propiloxilo, isopropiloxilo, n-butiloxilo, isobutiloxilo, sec-butiloxilo, terc-butiloxilo, n-pentiloxilo, n-hexiloxilo, n-heptiloxilo, n-octiloxilo, n-nonaniloxilo e n-decaniloxilo. Os exemplos preferidos incluem alquiloxilo C1-C6. Em particular, é preferido o alquiloxilo C1-C3.

Como aqui utilizado, os exemplos do "alquiloxialquilo" incluem metiloximetilo, metiloxietilo, metiloxipropilo, etiloximetilo, etiloxietilo, e etiloxipropilo. Os exemplos preferidos incluem alquiloxilo C1-C6 alquilo C1-C6. Em particular é preferido o alquiloxi C1-C3-alquilo C1-C4.

Como aqui utilizado, exemplos do "alquiloxicarbonilo" incluem metiloxicarbonilo, etiloxicarbonilo, n-propiloxicarbonilo, isopropiloxicarbonilo, n-butiloxicarbonilo, t-butiloxicarbonilo e n-pentiloxicarbonilo. Os exemplos preferidos incluem alquiloxi C1-C6-carbonilo. Em particular, é preferido o alquiloxi C1-C3-carbonilo.

Como aqui utilizado, os exemplos do "alquilcarbonilo" incluem metilcarbonilo, etilcarbonilo, n-propilcarbonilo, isopropilcarbonilo, n-butilcarbonilo, t-butilcarbonilo e n-pentilcarbonilo. Os exemplos preferidos incluem alquil C1-C6-carbonilo. Em particular, é preferido o alquil C1-C3-carbonilo.

Como aqui utilizado, os exemplos do "haloalquiloxilo" incluem trifluorometiloxilo, triclorometiloxilo, difluoroetiloxilo, trifluoroetiloxilo, dicloroetiloxilo e tricloroetiloxilo. Os exemplos preferidos incluem halo-alquiloxilo C1-C6. Em particular, é preferido o halo-alquiloxilo C1-C3. Os exemplos muito preferidos incluem trifluorometiloxilo.

Como aqui utilizado, os exemplos do "aminocarbonilalquilo" incluem aminocarbonilmetilo, aminocarboniletilo, aminocarbonilpropilo e aminocarbonilbutilo. Os exemplos preferidos incluem aminocarbonil-alquilo C1-C6. Em particular, é preferido o aminocarbonil-alquilo C1-C3.

Como aqui utilizado, os exemplos do "aminocarbonilalquiloxilo" incluem aminocarbonilmetiloxilo, aminocarboniletiloxilo, aminocarbonilpropiloxilo e aminocarbonilbutiloxilo. Os exemplos preferidos incluem aminocarbonil-alquiloxilo C1-C6. Em particular, é preferido o aminocarbonil-alquiloxilo C1-C3.

Como aqui utilizado, os exemplos do "hidroxialquilo" incluem hidroximetilo, hidroxietilo, hidroxipropilo e hidroxibutilo. Os exemplos preferidos incluem hidroxi-alquilo C1-C6. Em particular, é preferido o hidroxi-alquilo C1-C3.

Como aqui utilizado, os exemplos do "alquiltio" incluem metiltio, etiltio, propiltio e butiltio. Os exemplos preferidos incluem alquiltio C1-C6. Em particular, é preferido o alquiltio C1-C3.

Como aqui utilizado, o "alquileno", o qual é utilizado sozinho ou em associação com outro termo, inclui um grupo hidrocarboneto bivalente linear ou ramificado possuindo 1 a 4 átomo(s) de carbono. Os exemplos incluem metileno, etileno, propileno e butileno. Os exemplos preferidos incluem alquileno C1-C3. Em particular, é preferido o alquileno C1-C2.

O "alquileno, o qual pode estar intervalado com -O- ou $-N(R^{11})-$" em Z inclui $-CH_2-O-$, $-O-CH_2-$, $-CH_2-N(R^{11})-$, $-N(R^{11})-CH_2-$, $-(CH_2)_2-O-$, $-O-(CH_2)_2-$, $-(CH_2)_2-N(R^{11})-$ e $-N(R^{11})-(CH_2)_2-$. Em particular, são preferidos os $-O-CH_2-$, $-N(R^{11})-CH_2-$, $-O-(CH_2)_2-$ e $-N(R^{11})-(CH_2)_2-$.

O "alquileno, o qual pode estar intervalado com -O-, -S- ou $-N(R^{12})-$" em X inclui $-CH_2-O-$, $-O-CH_2-$, $-CH_2-S-$, $-S-CH_2-$, $-CH_2-N(R^{12})-$, $-N(R^{12})-CH_2-$, $-(CH_2)_2-O-$, $-O-(CH_2)_2-$, $-(CH_2)_2-S-$, $-S-(CH_2)_2-$, $-(CH_2)_2-N(R^{12})-$ e $-N(R^{12})-(CH_2)_2-$.

O "alquileno, o qual pode estar intervalado com -O-, -S- ou $-N(R^{9})-$" em Y inclui $-CH_2-O-$, $-O-CH_2-$, $-CH_2-S-$, $-S-CH_2-$, $-CH_2-N(R^{9})-$, $-N(R^{9})-CH_2-$, $-(CH_2)_2-O-$, $-O(CH_2)_2-$, $-(CH_2)_2-S-$, $-S-(CH_2)_2-$, $-(CH_2)_2-N(R^{9})-$, $-N(R^{9})-(CH_2)_2-$ e $-O-CH(CH_3)-$.

Como aqui utilizado, o "cicloalquilo", o qual é utilizado sozinho ou em associação com outro termo, inclui cicloalquilo possuindo 3 a 8 átomo(s) de carbono. Os exemplos incluem ciclopropilo, ciclobutilo, ciclopentilo, ciclo-hexilo,

ciclo-heptilo e ciclooctilo. Os exemplos preferidos incluem cicloalquilo C5-C6.

Como aqui utilizado, o "alcenilo" inclui um hidrocarboneto monovalente linear ou ramificado possuindo 2 a 8 átomo(s) de carbono e possuindo 1 ou 2 ou mais ligações duplas. O alcenilo pode ter uma ligação tripla numa cadeia. Os exemplos incluem vinilo, alilo, 1-propenilo, 2-propenilo e os vários isómeros de butenilo. Os exemplos preferidos incluem alcenilo C2-C6. Os exemplos mais preferidos incluem alcenilo C2-C4.

Como aqui utilizado, os exemplos do "alceniloxilo" incluem viniloxilo, aliloxilo, 1-propeniloxilo, 2-propeniloxilo e os vários buteniloxilos. Os exemplos preferidos incluem alceniloxilo C2-C6. Em particular, é preferido o alceniloxilo C2-C4.

Como aqui utilizado, os exemplos do "alceniloxicarbonilo" incluem viniloxicarbonilo, aliloxicarbonilo, 1-propeniloxicarbonilo, 2-propeniloxicarbonilo e os vários buteniloxicarbonilos. Os exemplos preferidos incluem alceniloxi C2-C6-carbonilo. Em particular, é preferido o alceniloxi C2-C4-carbonilo.

Como aqui utilizado, o "alcinilo" inclui um grupo hidrocarboneto monovalente linear ou ramificado possuindo 2 a 8 átomo(s) de carbono e possuindo 1 ou 2 ou mais ligações triplas. Os exemplos incluem etilnilo, 1-propinilo, 2-propinilo, 1-butinilo, 2-butinilo, 3-butinilo, 1-pentinilo, 2-pentinilo e os vários isómeros de pentinilo. Os exemplos preferidos incluem alcinilo C2-C6. Os exemplos mais preferidos incluem alcinilo C2-C4.

Como aqui utilizado, os exemplos do "alciniloxilo" incluem etiniloxilo, propiniloxilo, butiniloxilo e pentiniloxilo. Os exemplos preferidos incluem alciniloxilo C2-C6. Em particular, é preferido o alciniloxilo C2-C4.

Como aqui utilizado, o "arilo", o qual é utilizado sozinho ou em associação com outro termo, inclui um hidrocarboneto cíclico aromático monocíclico ou fundido. Os exemplos incluem fenilo, 1-naftilo, 2-naftilo e antrilo. O fenilo, 1-naftilo e 2-naftilo são preferidos. Em particular, é preferido o fenilo.

Como aqui utilizado, o "aralquilo" inclui o "alquilo" substituído com um ou dois ou mais de "arilo", e estes podem estar substituído em todas as posições possíveis. Os exemplos incluem benzilo, feniletilo (*e. g.*, 2-feniletilo, etc.), fenilpropilo (*e. g.*, 3-fenilpropilo, etc.), naftilmetilo (*e. g.*, 1-naftilmetilo, 2-naftilmetilo, etc.) e antrilmetilo (*e. g.*, 9-antrilmetilo, etc.). Os exemplos preferidos incluem benzilo e feniletilo.

Como aqui utilizado, os exemplos do "aralquiloxilo" incluem benziloxilo, feniletiloxilo (*e. g.*, 2-feniletiloxilo, etc.), fenilpropiloxilo (*e g.*, 3-fenilpropiloxilo, etc.), naftilmetiloxilo (*e. g.*, 1-naftilmetilo, 2-naftilmetiloxilo, etc.), antrilmetiloxilo (*e. g.*, 9-antrilmetiloxilo, etc.). Os exemplos preferidos incluem benziloxilo e feniletiloxilo.

Como aqui utilizado, os exemplos do "aralquiloxicarbonilo" incluem benziloxicarbonilo, feniletiloxicarbonilo (*e. g.*, 2-feniletiloxicarbonilo, etc.), fenilpropiloxicarbonilo (*e. g.*, 3-fenilpropiloxicarbonilo, etc.), naftilmetiloxicarbonilo (*e. g.*, 1-naftilmetilo, 2-naftilmetiloxicarbonilo,etc.),

antrilmetiloxicarbonilo (*e. g.*, 9-antrilmetiloxicarbonilo, etc.). Os exemplos preferidos incluem benziloxicarbonilo e feniletiloxicarbonilo.

Como aqui utilizado, o termo "grupo heterocíclico não aromático", o qual é utilizado sozinho ou em associação com outro termo, inclui um anel não aromático de 5 a 7 membros contendo um ou mais arbitrariamente seleccionados de um átomo de oxigénio, um átomo de enxofre ou um átomo de azoto num anel, e um grupo derivado de um anel no qual estão ali fundidos um ou mais de outros "grupos heterocíclicos não aromáticos" ou "heteroarilos". Os exemplos incluem pirrolidinilo (*e. g.*, 1-pirrolidinilo, 2-pirolidinilo), pirrolinilo (*e. g.*, 3-pirrolinilo), imidazolidinilo (*e. g.*, 2-imidazolidinilo), imidazolinilo (*e. g.*, imidazolinilo), pirazolidinilo (*e. g.*, 1-pirazolidinilo, 2-pirazolidinilo), pirazolinilo (*e. g.*, pirazolinilo), piperidilo (*e. g.*, piperidino, 2-piperidilo), piperazinilo (*e. g.*, 1-piperazinilo, 2-piperazinilo), indolinilo (*e. g.*, 1-indolinilo), isoindolinilo (*e. g.*, isoindolinilo), morfolinilo (*e. g.*, morfolino, 2-morfolinilo, 3-morfolinilo), tetra-hidrofuranilo, di-hidropiranilo, tetra-hidropiranilo, dioxolanilo, tetra-hidrotienilo, di-hidrotiopiranilo, tetra-hidrotiofuranilo, deca-hidroisoquinolinilo, azepinilo, oxepinilo, di-hidrooxepinilo, tetra-hidrooxepinilo, oxepanilo, 4,5,6,7-tetra-hidrotieno[3,2]piridilo, 2-oxa-5-aza-biciclo[2.2.1]hepta-5-ilo e hexa-hidropirazil[2.1-b][1, 3]ozadin-8-ilo.

Como o "grupo heterocíclico não aromático" em R^{19} são preferidos pirrodilinilo (*e. g.*, 1-pirrodilinilo. 2-pirrolidinilo), piperidilo (*e. g.*, piperidino, 2-piperidilo),

piperazinilo (*e. g.*, 1-piperazinilo), morfolinilo (*e. g.*, morfolino, 3-morfolinilo) e tetra-hidrofuranilo.

Como aqui utilizado, a expressão "grupo heterocíclico não aromático contendo azoto", o qual é utilizado sozinho ou em associação com outro termo, inclui um anel não aromático de 4 a 7 membros contendo pelo menos um átomo de azoto num anel e contendo, ainda opcionalmente, um ou mais átomos arbitrariamente seleccionados de um átomo de oxigénio e um átomo de enxofre num anel, ou um grupo derivado de um anel no qual estão fundidos dois ou mais daqueles. Os exemplos incluem azetidinilo (*e. g.*, 1-azetidinilo, 2-azetidinilo, 3-azetidinilo), pirrolidinilo (*e. g.*, 1-pirrolidinilo, 2-pirrolidinilo, 3-pirrolidinilo), pirrolinilo (*e. g.*, 3-pirrolinilo), imidazolidinilo (*e. g.*, 2-imidazolidinilo), imidazolinilo (*e. g.*, imidazolinilo), pirazolidinilo (*e. g.*, 1-pirazolidinilo, 2-pirazolidinilo), pirazolinilo (*e. g.*, pirazolinilo), piperidilo (*e. g.*, piperidino, 2-piperidilo, 3-piperidilo, 4-piperidilo), piperazinilo (*e. g.*, 1-piperazinilo, 2-piperazinilo), indolinilo (*e. g.*, 1-indolinilo), isoindolinilo (*e. g.*, isoindolinilo), morfolinilo (*e. g.*, morfolino, 2-morfolinilo, 3-morfolinilo), 1,4-tiazinilo (*e. g.*, 1,4-tiazin-1-ilo, 1,4-tiazin-2-ilo), tiomorfolinilo (*e. g.*, 1-tiomorfolinilo, 2-tiomorfolinilo), deca-hidroisoquinolilo (*e. g.*, 2-deca-hidroisoquinolilo), azepinilo (*e. g.*, 1-azepinilo), diazepinilo, 4,5,6,7-tetra-hidrotieno[3,2]piridilo, 2-oxa-5-aza-biciclo[2.2.1]hept-5-ilo e hexa-hidropirazil[2.1-b][1,3]oxazin-8-ilo.

Como o "grupo heterocíclico não aromático contendo azoto" em R^1 e R^{17} são preferidos o azetidinilo (*e. g.*, 1-azetidinilo, 2-azetidinilo, 3-azetidinilo), pirrolidinilo (*e. g.*,

1-pirrolidinilo, 2-pirrolidinilo, 3-pirrolidinilo) e piperidilo (*e. g.*, piperidino, 2-piperidilo, 3-piperidilo, 4-piperidilo).

Como o "grupo heterocíclico não aromático contendo azoto" em W^1 são preferidos o azetidinilo (*e. g.*, 1-azetidinilo, 2-azetidinilo, 3-azetidinilo), pirrolidinilo (*e. g.*, 1-pirrolidinilo, 2-pirrolidinilo, 3-pirrolidinilo), piperidilo (*e. g.*, piperidino, 2-piperidilo, 3-piperidilo, 4-piperidilo), piperazinilo (*e. g.*, 1-piperazinilo) e morfolinilo (*e. g.*, morfolino, 3-morfolinilo).

Como o "grupo heterocíclico não aromático contendo azoto" no grupo substituinte A são preferidos o pirrolidinilo (*e. g.*, 1-pirrolidinilo, 2-pirrolidinilo, 3-pirrolidinilo), piperidilo (*e. g.*, piperidino, 2-piperidilo, 3-piperidilo, 4-piperidilo), piperazinilo (*e. g.*, 1-piperazinilo, 2-piperazinilo), morfolinilo (*e. g.*, morfolino, 2-morfolinilo, 3-morfolinilo), tiomorfolinilo (*e. g.*, 1-tiomorfolinilo, 2-tiomorfolinilo), deca-hidroisoquinolilo (*e. g.*, 2-deca-hidroisoquinolilo), azepinilo (*e. g.*, 1-azepinilo), diazepinilo, 4,5,6,7-tetra-hidrotieno[3,2]piridilo, 2-oxa-5-aza-biciclo[2.2.1]hept-5-ilo e hexa-hidropirazil[2.1-b][1,3]oxazin-8-ilo.

Como aqui utilizado, o "heteroarilo", o qual é utilizado sozinho ou em associação com outro termo, inclui um grupo aromático de 5 a 6 membros contendo um ou mais de arbitrariamente seleccionados de um átomo de oxigénio, um átomo de enxofre e um átomo de azoto num anel. Este pode estar fundido com o "cicloalquilo", o "arilo", o "grupo heterocíclico não aromático" ou outro heteroarilo em todas as posições possíveis. Quando o heteroarilo é qualquer um de um monociclo e um ciclo fundido, ele pode ligar-se em todas as posições possíveis. Os

exemplos incluem pirrolilo (*e. g.*, 1-pirrolilo, 2-pirrolilo, 3-pirrolilo), furilo (*e. g.*, 2-furilo, 3-furilo), tienilo (*e. g.*, 2-tienilo, 3-tienilo), imidazolilo (*e. g.*, 2-imidazolilo, 4-imidazolilo), pirazolilo (*e. g.*, 1-pirazolilo, 3-pirazolilo), isotiazolilo (*e. g.*, 3-isotiazolilo), isooxazolilo (*e. g.*, 3-isooxazolilo), oxazolilo (*e. g.*, 2-oxazolilo), tiazolilo (*e. g.*, 2-tiazolilo, 5-tiazolilo), piridilo (*e. g.*, 2-piridilo, 3-piridilo, 4-piridilo), pirazinilo (*e. g.*, 2-pirazinilo), pirimidinilo (*e. g.*, 2-pirimidinilo, 4-pirimidinilo), piridazinilo (*e. g.*, 3-piridazinilo), triazolilo, tetrazolilo (*e. g.*, 1H-tetrazolilo), oxadiazolilo (*e. g.*, 1,3,4-oxadiazolilo), tiadiazolilo (*e. g.*, 1,3,4-tiadiazolilo), indolidinilo (*e. g.*, 2-indolidinilo, 6-indolidinilo), isoindolilo (*e. g.*, 2-isoindolilo), indolilo (*e. g.*, 1-indolilo, 2-indolilo, 3-indolilo), indazolilo (*e. g.*, 3-indazolilo), purinilo (*e. g.*, 8-purinilo), quinolizinilo (*e. g.*, 2-quinolizinilo), isoquinolilo (*e. g.*, 3-isoquinolilo), quinolilo (*e. g.*, 2-quinolilo, 5-quinolilo), ftalazinilo (*e. g.*, 1-ftalazinilo), naftiridinilo (*e. g.*, 2-naftiridinilo), quinolanilo (*e. g.*, 2-quinolanilo), quinazolinilo (*e. g.*, 2-quinazolinilo), cinolinilo (*e. g.*, 3-cinolinilo), pteridinilo (*e. g.*, 2-pteridinilo), carbazolilo (*e. g.*, 2-carbazolilo, 4-carbazolilo), fenantridinilo (*e. g.*, 2-fenantridinilo, 3-fenantridinilo), acridinilo (*e. g.*, 1-acridinilo, 2-acridinilo), dibenzofuranilo (*e. g.*, 1-dibenzofuranilo, 2-dibenzofuranilo), benzoimidazolilo (*e. g.*, 2-benzoimidazolilo), benzoisooxazolilo (*e. g.*, 3-benzoisooxazolilo), benzooxazolilo (*e. g.*, 2-benzooxazolilo), benzooxadiazolilo (*e. g.*, 4-benzooxadiazolilo), benzoisotiazolilo (*e. g.*, 3-benzoisotiazolilo), benzotiazolilo (*e. g.*, 2-benzotiazolilo), benzofurilo (*e. g.*, 3-benzofurilo), benzotienilo (*e. g.*, 2-benzotienilo), 4,5-di-hidronafto[1,2-

d]tiazolilo, 4H-cromeno[4,3-d]tiazolilo, 4H-tiocromeno[4,3-d]tiazolilo, 4,5-di-hidrotiazolo[5,4-c]quinolilo, 8H-indeno[1,2-d]tiazolilo e 5,6-di-hidro-4H-3-tia-1-aza-benzo[e]azulenilo.

Como o "heteroarilo" em R^2 são preferidos o piridilo, furilo, tienilo, tiazolilo, oxazolilo, tiadiazolilo, oxadiazolilo e triazolilo. Os exemplos mais preferidos incluem piridilo, furilo, tienilo, tiazolilo.

Como o "heteroarilo" em R^8 são preferidos o piridilo, furilo, tienilo, tiazolilo, oxazolilo, tiadiazolilo, oxadiazolilo e triazolilo. Os exemplos mais preferidos incluem piridilo, furilo, tienilo e tiazolilo.

Como o "heteroarilo" em R^{19} são preferidos o piridilo, furilo e tienilo.

Como o "heteroarilo" em W^1 são preferidos o pirrolilo, imidazolilo, pirazolilo, triazolilo e tetrazolilo.

Como aqui utilizado, o "heteroarilalquilo" inclui o "alquilo" no qual um ou dois ou mais dos "heteroarilos" estão substituídos numa posição arbitrária daquele, e estes podem estar substituídos em todas as posições possíveis. Os exemplos incluem tienilmetilo (*e. g.*, 2-tienilmetilo), tieniletilo (*e. g.*, 2-(tiofen-2-il)etilo), furilmetilo (*e. g.*, 2-furilmetilo), furiletilo (*e. g.*, 2-(furan-2-il)etilo), pirrolilmetilo (*e. g.*, 2-pirrolilmetilo), pirroliletilo (*e. g.*, 2-(pirrol-2-il)etilo), imidazolilmetilo (*e. g.*, 2-imidazolilmetilo, 4-imidazolilmetilo), imidazoliletilo (*e. g.*, 2-(imidazol-2-il)etilo), pirazolilmetilo (*e. g.*, 3-pirazolilmetilo), pirazoliletilo (*e. g.*, 2-(pirazol-3-

il)etilo), tiazolilmetilo (*e. g.*, 2-tiazolilmetilo), tiazoliletilo (*e. g.*, 2-(tiazol-2-il)etilo), isotiazolilmetilo (*e. g.*, 3-isotiazolilmetilo), isooxazolilmetilo (*e. g.*, 3-isooxazolilmetilo), oxazolilmetilo (*e. g.*, 2-oxazolilmetilo), oxazoliletilo (*e. g.*, 2-(oxazol-2-il)etilo), piridilmetilo (*e. g.*, 2-piridilmetilo, 3-piridilmetilo, 4-piridiilmetilo) e piridiletilo (*e. g.*, 2-piridiletilo).

Como aqui utilizado, um termo do "acilo", o qual é utilizado sozinho ou em associação com outro termo, inclui alquilcarbonilo no qual uma parte de alquilo é o "alquilo", haloalquilcarbonilo no qual uma parte de haloalquilo é o "haloalquilo", alcenilcarbonilo no qual uma parte de alcenilo é o "alcenilo", aralquilcarbonilo no qual uma parte de aralquilo é o "aralquilo" e arilcarbonilo no qual uma parte de arilo é o "arilo". Os exemplos incluem acetilo, propionilo, butiroílo, trifluorometilcarbonilo, vinilcarbonilo, fenilacetilo e benzoílo. O "alquilo", o "alcenilo" e o "arilo" pode estar substituído com cada substituinte descrito abaixo.

Como o "acilo" em R^{10} e R^{11} são preferidos o acetilo, benzoílo e fenilacetilo.

Como o "acilo" em R^{12} e R^{13} são preferidos o acetilo, benzoílo e fenilacetilo.

Como o "acilo" em R^{9} são preferidos o acetilo, benzoílo e fenilacetilo.

Como aqui utilizado, os exemplos do "aciloxilo" incluem acetiloxilo, propioniloxilo e benzoiloxilo.

Como aqui utilizado, um termo do "amino opcionalmente substituído", o qual é utilizado sozinho ou em associação com outro termo, inclui amino opcionalmente substituído com o "alquilo" opcionalmente substituído com um substituinte seleccionado do grupo substituinte A, o "haloalquilo", o "alcenilo", o "alcinilo", o "alquilsulfonilo", o "alquilsulfonilalquilo", o "alquiloxicarbonilo", o "aminocarboniloxialquilo", o "alquiloxilo", o "alquiloxialquilo" opcionalmente substituído com um substituinte seleccionado do grupo substituinte A, o "cicloalquilo" opcionalmente substituído com um substituinte seleccionado do grupo substituinte A, o "arilo" opcionalmente substituído com um substituinte seleccionado do grupo substituinte G consistindo de alquilo, alcenilo e aralquilo, o "aralquilo", o "heteroarilo", o "heteroarilalquilo", o "acilo", o "aminocarbonilalquilo" opcionalmente substituído com um substituinte seleccionado do grupo substituinte G, o "aminoalquilcarbonilo" opcionalmente substituído com um substituinte seleccionado do grupo substituinte G, "alceniloxicarbonilo" no qual uma parte alceniloxilo é o "alceniloxilo", e "aralquiloxicarbonilo" no qual uma parte aralquiloxilo é o "aralquiloxilo" em um ou dois sítio(s). Os exemplos incluem amino, metilamino, dimetilamino, etilmetilamino, dietilamino, etilmetilamino, diisopropilamino, benzilamino, acetilamino, trifluorometilcarbonilo, benzoilamino, metiloxicarbonilamino, etiloxicarbonilamino, n-propiloxicarbonilamino, isopropiloxicarbonilamino, n-butiloxilo, isobutiloxicarbonilamino, sec-butiloxicarbonilamino, terc-butiloxicarbonilamino, aliloxicarbonilamino, benziloxicarbonilamino, ciclopentilamino e ciclo-hexilamino.

Como um substituinte do "amino opcionalmente substituído" em R^3 e R^4 são preferidos o alquilo, acilo e semelhantes.

Como um substituinte do "amino opcionalmente substituído" em R^6 e R^7 são preferidos o alquilo e semelhantes.

Como um substituinte do "amino opcionalmente substituído" e do "aminocarbonilo opcionalmente substituído" no grupo substituinte A, alquilo, alcenilo, alcinilo, arilo opcionalmente substituído com um substituinte seleccionado do grupo substituinte I, aralquilo, alquiloxilo, hidroxialquilo, hidroxialquiloxialquilo, haloalquilo, aminoalquilo opcionalmente substituído com 1 ou 2 alquilo(s), alquilsulfonilo, alquilsulfonilalquilo, alquilcarbonilo opcionalmente substituído com halogéneo ou alquiloxilo, alquiloxicarbonilo, cicloalquilo opcionalmente substituído com um substituinte seleccionado do grupo substituinte I, carboxialquilo, aminocarbonilalquilo opcionalmente substituído com um substituinte seleccionado do grupo substituinte G, aminocarboniloxialquilo opcionalmente substituído com um substituinte seleccionado do grupo substituinte G, alquiloxialquilo, alquiltioalquilo, alquilcarbonilaminoalquilo, alquilsulfonilaminoalquilo, alquilsulfonil(alquil)aminoalquilo, alquiloxicarbonilalquilo, alquiltio(hidroxi)alquilo, cicloalquilalquilo, cianoalquilo, aminoalquilcarbonilo opcionalmente substituído com um substituinte seleccionado do grupo substituinte G, heteroarilo opcionalmente substituído com um substituinte seleccionado do grupo substituinte G, heteroarilalquilo, hidroxialquiloxialquilo, um grupo heterocíclico não aromático opcionalmente substituído com um substituinte seleccionado do grupo substituinte I e um alquilo heterocíclico não aromático

opcionalmente substituído com um substituinte seleccionado do grupo substituinte I.

Aqui, como um substituinte no "aminocarbonilo opcionalmente substituído" são preferidos o alquilo, alcenilo, aralquilo e semelhantes. Em particular, é preferido o alquilo.

Como um substituinte no "aminocarbonilo opcionalmente substituído" num grupo substituinte B são preferidos o alquilo, alcenilo, aralquilo e semelhantes.

Como um substituinte no "aminocarbonilo opcionalmente substituído" num grupo substituinte D são preferidos o alquilo, alcenilo, aralquilo e semelhantes.

Como um substituinte no "aminocarbonilo opcionalmente substituído" num grupo substituinte E são preferidos o alquilo, alcenilo, aralquilo e semelhantes.

Como um substituinte no "aminocarbonilo opcionalmente substituído" num grupo substituinte H são preferidos o alquilo, alcenilo, aralquilo e semelhantes.

Aqui, como um substituinte no "aminocarbonilalquilo opcionalmente substituído" são preferidos o alquilo, alcenilo aralquilo e semelhantes. Em particular, é preferido o alquilo.

Como um substituinte no "aminocarbonilalquilo opcionalmente substituído" num grupo substituinte C são preferidos o alquilalcenilo, aralquilo e semelhantes.

Aqui, como um substituinte no "aminocarboniloxialquilo opcionalmente substituído" são preferidos o alquilo, alcenilo, aralquilo e semelhantes. Em particular, é preferido o alquilo.

Como um substituinte no "aminocarboniloxialquilo opcionalmente substituído" num grupo substituinte C são preferidos o alquilo, alcenilo, aralquilo e semelhantes.

Aqui, como um substituinte no "aminoalquilcarbonilo opcionalmente substituído" são preferidos o alquilo, alcenilo, aralquilo e semelhantes. Em particular, é preferido o alquilo.

Como um substituinte no "aminoalquilcarbonilo opcionalmente substituído" num grupo substituinte C são preferidos o alquilo, alcenilo, aralquilo e semelhantes.

Aqui, um termo do "ureido opcionalmente substituído" inclui ureido opcionalmente substituído com o "alquilo", o "cicloalquilo", o "arilo", o "aralquilo", o "heteroarilo", o "heteroarilalquilo", o "acilo", cianoalquilo ou alquiloxialquilo em um ou dois ou mais sítios.

Aqui, um termo do "guanidino opcionalmente substituído" inclui guanidino opcionalmente substituído com o "alquilo", o "cicloalquilo", o "arilo", o "aralquilo", o "heteroarilo", o "heteroarilalquilo", o "acilo", ciano, cianoalquilo ou alquiloxialquilo em um ou dois ou mais sítios.

Aqui, os exemplos de um substituinte no "alquilo opcionalmente substituído" incluem amino opcionalmente substituído, um grupo heterocíclico não aromático contendo azoto opcionalmente substituído, carbonilo heterocíclico não aromático

contendo azoto opcionalmente substituído, alquilo, alquiloxilo, ciano, alquilsulfonilo, cicloalquilo, alcenilo, heteroarilo, heteroariloxilo, hidroxilo, mercapto, alquiltio, halogéneo, nitro, carboxilo, alquiloxicarbonilo, hidroxialquilo, haloalquilo, haloalquiloxilo, alquilcarboniloxilo, carbamoiloxilo, aminocarbonilo opcionalmente substituído, aminocarbonilalquiloxilo, acilo, aciloxilo, ariloxilo, aralquilo, aralquiloxilo, guanidino opcionalmente substituído, um grupo azo e ureido opcionalmente substituído. Estes podem estar substituídos com um ou mais substituinte(s) em todas as posições possíveis.

Como um substituinte no "alquilo opcionalmente substituído" em R^1, R^{17} e R^{19} são preferidos um substituinte seleccionado do grupo substituinte A, alquiloxilo, ciano, halogéneo, heteroarilo e semelhantes. Em particular, são preferidos o amino opcionalmente substituído com um substituinte seleccionado do grupo substituinte C e um grupo heterocíclico não aromático contendo azoto opcionalmente substituído com um substituinte seleccionado do grupo substituinte D.

Como um substituinte do "alquilo opcionalmente substituído" em R^2 são preferidos um substituinte seleccionado do grupo substituinte A, alquiloxilo, alquilcarbonilo e halogéneo. Em particular são preferidos o hidroxilo, alquiloxilo e halogéneo.

Como um substituinte do "alquilo opcionalmente substituído" em R^3 e R^4 são preferidos o alquiloxilo, alquiloxicarbonilo, aminocarbonilo, ciano e semelhantes.

Como um substituinte do "alquilo opcionalmente substituído" em R^6 e R^7 são preferidos o alquiloxilo, alquiloxicarbonilo, aminocarbonilo, ciano, hidroxilo e semelhantes.

Como um substituinte do "alquilo opcionalmente substituído" em R^{18} são preferidos o hidroxilo, alquiloxilo, halogéneo, ciano e semelhantes.

Como um substituinte do "alquilo opcionalmente substituído" em R^{20} são preferidos o hidroxilo, alquiloxilo, halogéneo, ciano e semelhantes.

Aqui, os exemplos de um substituinte no "alcenilo opcionalmente substituído" e no "alcinilo opcionalmente substituído" incluem amino opcionalmente substituído, um grupo heterocíclico não aromático contendo azoto opcionalmente substituído, cicloalquilo, hidroxilo, alquiloxilo, mercapto, alquiltio, halogéneo, nitro, ciano, carboxilo, alquiloxicarbonilo, haloalquilo, haloalquiloxilo, aminocarbonilo opcionalmente substituído, acilo, aciloxilo, arilo, ariloxilo, aralquilo, aralquiloxilo, alquilsulfonilo, guanidino, um grupo azo, ureido opcionalmente substituído e semelhantes. Estes podem estar substituídos com um ou mais substituinte(s) em todas as posições possíveis.

Como um substituinte do "alcenilo opcionalmente substituído" em R^1 e R^{17} é preferido um substituinte seleccionado do grupo substituinte A. Em particular, são preferidos o amino opcionalmente substituído com um substituinte seleccionado do grupo substituinte C e um grupo heterocíclico não aromático contendo azoto opcionalmente substituído com um substituinte seleccionado do grupo substituinte D.

Como um substituinte do "alcenilo opcionalmente substituído" e do "alcinilo opcionalmente substituído" em R^2 são preferidos um substituinte seleccionado do grupo substituinte A, cicloalquilo, alquiloxilo e halogéneo. Em particular, são preferidos o hidroxilo, cicloalquilo, alquiloxilo e halogéneo.

Como um substituinte do "alcenilo opcionalmente substituído" e do "alcinilo opcionalmente substituído" em R^3 e R^4 são preferidos o alquiloxilo, alquiloxicarbonilo, aminocarbonilo, alquilo opcionalmente substituído com ciano e semelhantes, alquiloxilo, alquiloxicarbonilo, aminocarbonilo, alquiloxicarbonilo opcionalmente substituído com ciano e semelhantes, e aminocarbonilo opcionalmente substituído, e semelhantes.

Como um substituinte do "alcenilo opcionalmente substituído" e do "alcinilo opcionalmente substituído" em R^6 e R^7 são preferidos o alquiloxilo, alquiloxicarbonilo, aminocarbonilo, alquilo opcionalmente substituído com ciano e semelhantes, alquiloxilo, alquiloxicarbonilo, aminocarbonilo, alquiloxicarbonilo opcionalmente substituído com ciano e semelhantes, e aminocarbonilo opcionalmente substituído, e semelhantes.

Como um substituinte do "alcenilo opcionalmente substituído" e do "alcinilo opcionalmente substituído" em R^{18} são preferidos o hidroxilo, alquiloxilo, halogéneo, ciano e semelhantes.

Como um substituinte do "alcenilo opcionalmente substituído" e do "alcinilo opcionalmente substituído" em R^{20} são preferidos o hidroxilo, alquiloxilo, halogéneo, ciano e semelhantes.

Aqui, os exemplos de um substituinte no "cicloalquilo opcionalmente substituído" incluem alquiloxicarbonilo, aminocarbonilo opcionalmente substituído com um substituinte seleccionado do grupo substituinte G, ciano, alquilo opcionalmente substituído com um substituinte seleccionado do grupo substituinte M consistindo de ciano, hidroxilo, carboxilo, aminocarbonilo, alquiloxicarbonilo e alquiloxilo, alquilsulfonilo, alquilsulfonilalquilcarbonilo, cicloalquilo, hidroxilo, alquiloxilo, mercapto, alquiltio, halogéneo, nitro, carboxilo, haloalquilo, haloalquiloxilo, acilo, aciloxilo, arilo, ariloxilo (*e. g.*, feniloxilo), aralquilo, aralquiloxilo (*e. g.*, benziloxilo), um grupo heterocíclico não aromático contendo azoto, alquilcarbonilamino, aminocarboniloxilo, amino, oxo, guanidino, um grupo azo e ureido opcionalmente substituído.

Como um substituinte do "cicloalquilo opcionalmente substituído" no grupo substituinte C são preferidos os substituintes exemplificado no grupo substituinte I.

Aqui, os exemplos de um substituinte do "alquiloxilo opcionalmente substituído", do "alceniloxilo opcionalmente substituído" e do "alciniloxilo opcionalmente substituído" incluem cicloalquilo, alcenilo, hidroxilo, alquiloxilo, mercapto, alquiltio, halogéneo, nitro, ciano, carboxilo, alquiloxicarbonilo, haloalquilo, haloalquiloxilo, amino opcionalmente substituído, aminocarbonilo opcionalmente substituído, acilo, aciloxilo, um grupo heterocíclico não

aromático opcionalmente substituído, ariloxilo, aralquiloxilo, alquilsulfonilo, guanidino, um grupo azo e ureido opcionalmente substituído. Estes podem substituir um ou mais sítios de todas as posições possíveis. Os exemplos preferidos incluem halogéneo.

Como um substituinte do "alquiloxilo opcionalmente substituído" e do "alceniloxilo opcionalmente substituído" em R^3 e R^4 são preferidos o alquiloxilo, o amino opcionalmente substituído, um grupo heterocíclico não aromático opcionalmente substituído com um substituinte seleccionado do grupo substituinte D, ciano, e semelhantes.

Como um substituinte do "alquiloxilo opcionalmente substituído", do "alceniloxilo opcionalmente substituído" e do "alciniloxilo opcionalmente substituído" em R^5 é preferido um substituinte seleccionado do grupo substituinte E.

Como um substituinte do "alquiloxilo opcionalmente substituído", do "alceniloxilo opcionalmente substituído" e do "alciniloxilo opcionalmente substituído" em R^6 e R^7 são preferidos o alquiloxilo, ciano, alquiloxicarbonilo, aminocarbonilo opcionalmente substituído e semelhantes.

Aqui, os exemplos de um substituinte no "grupo heterocíclico não aromático opcionalmente substituído " incluem alquiloxicarbonilo, aminocarbonilo opcionalmente substituído com um substituinte seleccionado do grupo substituinte G, ciano, alquilo opcionalmente substituído com um substituinte seleccionado do grupo substituinte M consistindo de ciano, hidroxilo, carboxilo, aminocarbonilo, alquiloxicarbonilo, e alquiloxilo, alquilsulfonilo, alquilsulfonilalquilcarbonilo, cicloalquilo, hidroxilo, alquiloxilo, mercapto, alquiltio,

halogéneo, nitro, carboxilo, haloalquilo, haloalquiloxilo, acilo, aciloxilo, arilo, ariloxilo (*e. g.*, feniloxilo), aralquilo, aralquiloxilo (*e. g.*, benziloxilo), um grupo heterocíclico não aromático contendo azoto, alquilcarbonilamino, aminocarboniloxilo, amino, oxo, guanidino, um grupo azo e ureido opcionalmente substituído.

Aqui, os exemplos de um substituinte no "grupo heterocíclico não aromático contendo azoto opcionalmente substituído" incluem alquiloxicarbonilo, aminocarbonilo opcionalmente substituído com um substituinte seleccionado do grupo substituinte G, ciano, alquilo opcionalmente substituído com um substituinte seleccionado do grupo substituinte M consistindo de ciano, hidroxilo, carboxilo, aminocarbonilo, alquiloxicarbonilo e alquiloxilo, alquilsulfonilo, alquilsulfonilalquilcarbonilo, cicloalquilo, hidroxilo, alquiloxilo, mercapto, alquiltio, halogéneo, nitro, carboxilo, haloalquilo, haloalquiloxilo, acilo, aciloxilo, arilo, ariloxilo (*e. g.*, feniloxilo), aralquilo, aralquiloxilo (*e. g.*, benziloxilo), um grupo heterocíclico não aromático contendo azoto, alquilcarbonilamino, aminocarboniloxilo, amino opcionalmente substituído, oxo, guanidino, um grupo azo e ureido opcionalmente substituído.

Como um substituinte do "grupo heterocíclico não aromático contendo azoto opcionalmente substituído" em R^1 e R^{17} são preferidos o alquilo, alquiloxicarbonilo, aminocarbonilo opcionalmente substituído com um substituinte seleccionado do grupo substituinte G, ciano, oxo, amino, carboxilo, hidroxialquilo, cianoalquilo, alquiloxialquilo, alquilsulfonilo, alquilcarbonilo, alcenilcarbonilo, alquilsulfonilalquil-carbonilo, alquilcarbonilamino, alquilsulfonilamino,

carboxialquilo, alquiloxicarbonilalquilo e semelhantes. Em particular, são preferidos os substituintes exemplificados no grupo substituinte B.

Como um substituinte do "grupo heterocíclico não aromático contendo azoto opcionalmente substituído" em W^1 são preferidos o alquilo, alquiloxicarbonilo, aminocarbonilo opcionalmente substituído, ciano, hidroxialquilo, cianoalquilo, alquiloxialquilo, alquilsulfonilo, alquilcarbonilo, alcenilcarbonilo, alquilsulfonilalquilcarbonilo e semelhantes. Em particular, são preferidos os substituintes exemplificados no grupo substituinte J.

Como um substituinte do "grupo heterocíclico não aromático contendo azoto opcionalmente substituído" e do "carbonilo heterocíclico não aromático contendo azoto opcionalmente substituído" no grupo substituinte A é preferido um substituinte seleccionado do grupo substituinte D.

Aqui, os exemplos de um substituinte no "arilo opcionalmente substituído", no "fenilo opcionalmente substituído", no "heteroarilo opcionalmente substituído", no "piridilo opcionalmente substituído", no "furilo opcionalmente substituído", no "tienilo opcionalmente substituído", no "tiazolilo opcionalmente substituído", no "oxazolilo opcionalmente substituído", no "grupo heterocíclico não aromático opcionalmente substituído", no "alquilo heterocíclico não aromático opcionalmente substituído", no "cicloalquilo opcionalmente substituído", no "aralquilo opcionalmente substituído" e no "heteroarilalquilo opcionalmente substituído" incluem alquilo opcionalmente substituído (como um substituinte, halogéneo, hidroxilo, nitro, ciano, carboxilo, alquiloxilo,

alquiloxicarbonilo, acilo, etc.), cicloalquilo, alcenilo, alcinilo, hidroxilo, alquiloxilo, aralquiloxilo, mercapto, alquiltio, halogéneo, nitro, ciano, carboxilo, alquiloxicarbonilo, ariloxicarbonilo, haloalquilo, haloalquiloxilo, amino opcionalmente substituído, aminocarbonilo opcionalmente substituído, acilo, aciloxilo, arilo opcionalmente substituído (como um substituinte, halogéneo, hidroxilo, nitro, ciano, carboxilo, alquiloxilo, alquiloxicarbonilo, acilo, etc.), heteroarilo opcionalmente substituído (como um substituinte, halogéneo, hidroxilo, nitro, ciano, carboxilo, alquiloxilo, alquiloxicarbonilo, acilo, etc.), um grupo heterocíclico não aromático opcionalmente substituído (como um substituinte, halogéneo, hidroxilo, nitro, ciano, carboxilo, alquiloxilo, alquiloxicarbonilo, acilo, etc.), aralquilo opcionalmente substituído (como um substituinte, halogéneo, hidroxilo, nitro, ciano, carboxilo, alquiloxilo, alquiloxicarbonilo, acilo, etc.), alquilsulfonilo, guanidino, um grupo azo, -N= N-(fenilo opcionalmente substituído) e ureido opcionalmente substituído. Estes podem substituir uma ou mais de todas as posições possíveis.

Como um substituinte do "arilo opcionalmente substituído" em R^1 são preferidos os substituintes exemplificado no grupo substituinte I.

Como um substituinte do "arilo opcionalmente substituído" e do "heteroarilo opcionalmente substituído" em R^2 são preferidos o alquilo opcionalmente substituído com hidroxilo ou amino opcionalmente substituído, amino opcionalmente substituído, halogéneo e semelhantes. Em particular, é preferido o alquilo opcionalmente substituído com hidroxilo ou amino opcionalmente substituído.

Como um substituinte do "arilo opcionalmente substituído", do "heteroarilo opcionalmente substituído" e do "grupo heterocíclico não aromático opcionalmente substituído" em R^8 são preferidos o alquiloxicarbonilo, aminocarbonilo opcionalmente substituído, ciano, halogéneo, alquilo, alquiloxilo, alquiltio, haloalquilo e semelhantes. Em particular, são preferidos os substituintes exemplificados no grupo substituinte F.

Como um substituinte do "arilo opcionalmente substituído" e do "heteroarilo opcionalmente substituído" em R^{19} são preferidos o alquiloxicarbonilo, aminocarbonilo opcionalmente substituído, ciano, cianoalquilo, hidroxialquilo, aminocarbonilalquilo e semelhantes. Em particular, são preferidos os substituintes exemplificados no grupo substituinte I.

Como um substituinte do "heteroarilo opcionalmente substituído" em W^1 são preferidos o alquilo, hidroxilo, alquiloxilo e semelhantes. Em particular, são preferidos os substituintes exemplificados no grupo substituinte J.

Como um substituinte do "arilo opcionalmente substituído", do "heteroarilo opcionalmente substituído", do "grupo heterocíclico não aromático opcionalmente substituído" e do "alquilo heterocíclico não aromático opcionalmente substituído" num grupo substituinte C são preferidos os substituintes exemplificados no grupo substituinte I.

Aqui, a "composição farmacêutica útil para o tratamento de cancro" e a "terapêutica para um cancro" incluem terapêuticas para tumor cerebral (*e. g.*, glioblastoma), cancro de órgão urinário (*e. g.*, cancro da bexiga, cancro do rim), cancro genital (cancro da próstata, cancro do ovário, cancro do útero),

tumor linfóide, cancro do aparelho digestivo (*e. g.*, cancro do estômago, cancro do intestino grosso), cancro da faringe, cancro do pulmão (*e. g.*, cancro da glândula do pulmão, cancro das células pequenas do pulmão, cancro das células não pequenas do pulmão), cancro pancreático, cancro da mama, cancro da cabeça e pescoço, cancro do esófago e glândula tiróide. Em particular, a composição é de um modo preferido utilizada como terapêutica para o cancro da mama, tumor cerebral, cancro da bexiga, cancro do rim, cancro da próstata, cancro do ovário, cancro do útero, cancro do pulmão, cancro pancreático, cancro do intestino grosso e cancro da cabeça e pescoço.

A presente invenção inclui um método de tratamento ou prevenção de um cancro num mamífero no qual é necessário tratar ou prevenir um cancro, e o método compreende administrar uma quantidade terapeuticamente eficaz do composto da fórmula (I) ao mamífero. Um cancro que é de um modo preferido tratado é seleccionado de tumor cerebral (*e. g.*, glioblastoma), cancro de órgão urinário (*e. g.*, cancro da bexiga, cancro do rim), cancro genital (cancro da próstata, cancro do ovário, cancro do útero), tumor linfóide, cancro do aparelho digestivo (*e. g.*, cancro do estômago), cancro da faringe, cancro do pulmão, (*e. g.*, cancro da glândula do pulmão, cancro das células pequenas do pulmão, cancro das células não pequenas do pulmão), cancro pancreático, cancro da mama, cancro da cabeça e pescoço, cancro do esófago e glândula tiróide. Mais preferidos são o cancro da mama, tumor cerebral, cancro da bexiga, cancro do rim, cancro da próstata, cancro do ovário, cancro do útero, cancro do pulmão, cancro pancreático, cancro do intestino grosso e cancro da cabeça e pescoço.

Efeito da invenção

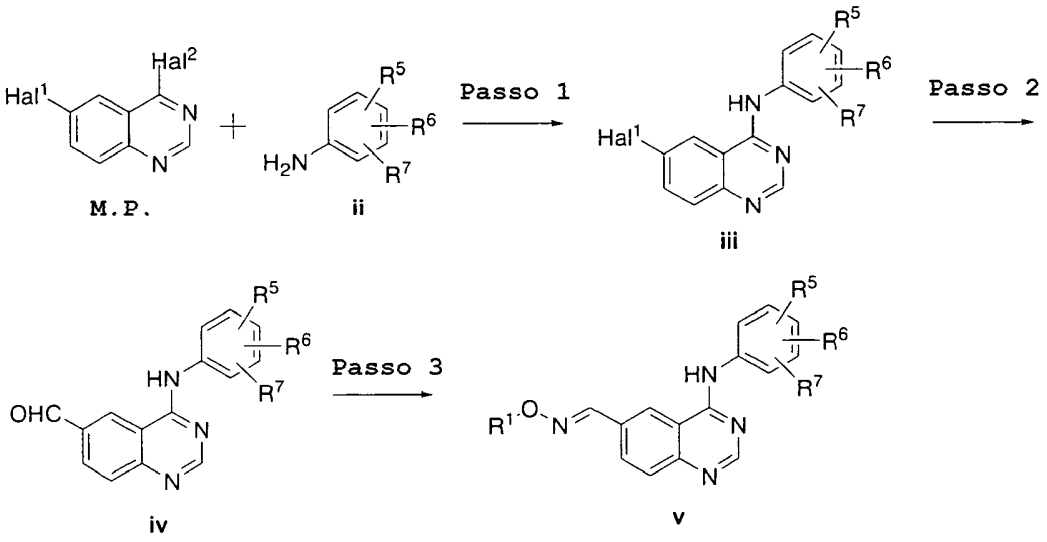
O presente composto tem uma excelente acção de inibição de um receptor de EGF e HER2, e tem segurança elevada (tem actividade inibidora de CYP reduzida) e é, por conseguinte, útil como um medicamento, *inter alia*, um agente terapêutico para um cancro.

Melhor modo para realizar a invenção

O presente composto (I) pode ser sintetizado por qualquer um dos métodos A a E descritos abaixo. Alternativamente, uma vez que é descrito um método de síntese de um derivado de quinazolina nos documentos WO 96/09294, WO 98/02434 e semelhantes, o presente composto (I) também pode ser sintetizado de acordo com o mesmo. Quando o composto tem um grupo que é afectado em cada reacção, o grupo pode ser protegido com um grupo de protecção adequado e pode ser desprotegido numa fase adequada. Além disso, quando uma matéria-prima, um reagente, um intermediário e um produto da reacção de cada passo pode formar um sal, o sal está incluído.

Método A

Fórmula química 25



em que Hal^1 e Hal^2 são, cada, independentemente halogéneo; R^1, R^5, R^6 e R^7 são como definidos em (1).

Passo 1

O primeiro passo é um passo de síntese de um composto (iii) fazendo reagir uma matéria-prima de partida (M.P.) que pode ser sintetizada de acordo com o método descrito no documento WO 96/09294 ou semelhantes, ou está comercialmente disponível, e um composto (ii) que pode ser sintetizado de acordo com o método descrito no documento WO 98/02434 ou semelhantes, ou está comercialmente disponível.

A matéria-prima de partida (M.P.) e o composto (ii) podem ser feitos reagir num solvente tais como tetra-hidrofurano,

acetonitrilo e semelhantes a 20 °C até aquecimento sob refluxo, de um modo preferido a 60 °C até aquecimento sob refluxo, para obter o composto (iii).

Passo 2

O segundo passo é um passo de inserção de monóxido de carbono no composto (iii) na presença de um catalisador de paládio para obter um composto (iv).

O composto (iii) pode ser feito reagir a 50 °C até 150 °C, de um modo preferido 70 °C até 90 °C sob atmosfera de monóxido de carbono num solvente tais como N,N-dimetilformamida, N,N-dimetilacetamida, N,N'-dimetilimidazolidinona, dimetilsulfóxido e semelhantes, na presença de uma fonte de hidrogénio tais como formato de sódio, hidreto de tributilestanho e semelhantes, um catalisador de paládio tais como diclorobis(trifenilfosfina)paládio, tetraquis(trifenilfosfina)-paládio, tris(dibenzilidenoacetona)dipaládio, [1,1'-bis(difenilfosfino)ferroceno]dicloropaládio, acetato de paládio+trifenilfosfina e semelhantes, e uma base tais como trietilamina, di(isopropil)etilamina e semelhantes para obter o composto (iv).

Passo 3

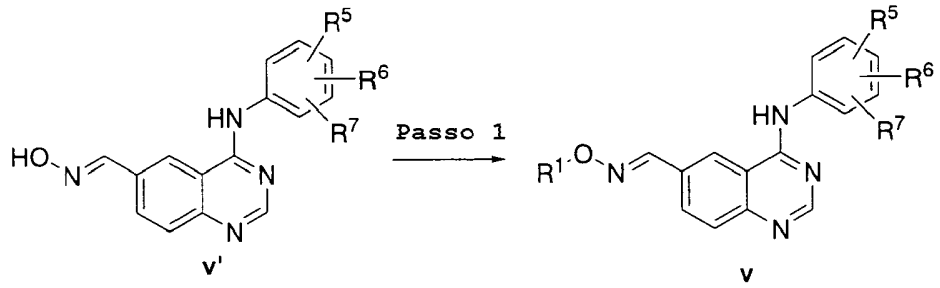
O terceiro passo é um passo de síntese de um composto alvo (v) fazendo reagir o composto (iv) e um composto

representado pela fórmula: R^1-O-NH_2 em que R^1 é como definido em (1).

A matéria-prima de partida (iv) e o composto representado pela fórmula: R^1-O-NH_2 em que R^1 é como definido em (1) ou um sal podem ser feitos reagir a 0 °C até aquecimento sob refluxo, de um modo preferido a 20 °C até 70 °C num solvente tais como tetra-hidrofurano, dioxano, metanol e semelhantes, ou num solvente misto daqueles e água, se for necessário, na presença de um ácido tais como ácido clorídrico, ácido sulfúrico, ácido p-toluenossulfónico, ácido metanossulfónico, ácido fórmico, ácido acético, ácido trifluoroacético e semelhantes para obter o composto (v).

Método B

Fórmula química 26



em que R^1, R^5, R^6 e R^7 são como definidos em (1).

Passo 1

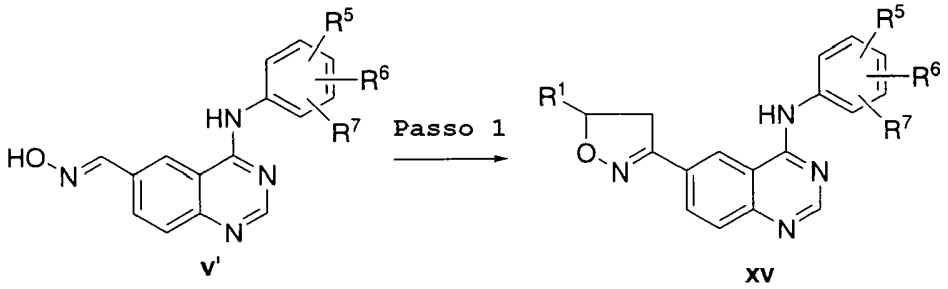
O primeiro passo é um passo de síntese de um composto alvo (v) fazendo reagir um composto (v') obtido fazendo reagir o

composto (iv) obtido no Método A com hidroxilamina, e um composto representado pela fórmula: R^1-Hal^3 em que Hal^3 é halogéneo; R^1 é como definido em (1).

O composto (v') e o composto representado pela fórmula: R^1-Hal^3 em que Hal^3 é halogéneo; R^1 é como definido em (1) podem ser dissolvidos num solvente tais como N,N-dimetilacetamida, N,N-dimetilacetamida, N,N'-dimetilimidazolidinona, dimetilsulfóxido e semelhantes, e feitos reagir a 50 °C até 150 °C, de um modo preferido 60 °C até 80 °C na presença de uma base tais como carbonato de potássio, carbonato de sódio e semelhantes para obter o composto (v).

Método C

Fórmula química 27



em que R^1, R^5, R^6 e R^7 são como definidos em (1).

Passo 1

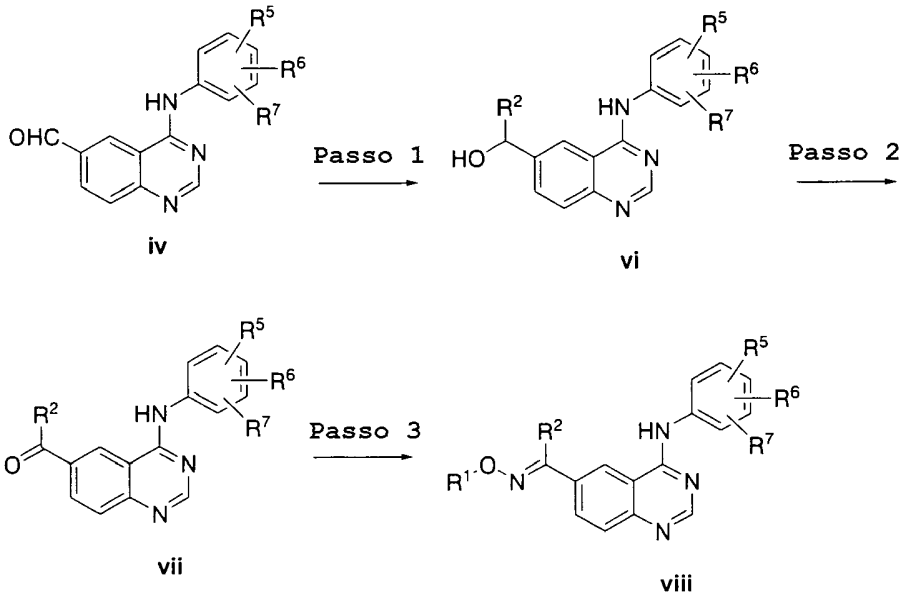
O primeiro passo é um passo de síntese de um composto alvo (xv) fazendo reagir um composto (v') obtido fazendo reagir

o composto (iv) obtido no Método A com hidroxilamina, e um composto representado pela fórmula: R^1-CH= CH_2 em que R^1 é como definido em (1).

O composto (xv) pode ser obtido dissolvendo o composto (v') num solvente tais como clorofórmio, diclorometano, 1,2-dicloroetano e semelhantes, e fazendo reagir com um agente oxidante à base de cloro tais como N-clorossuccinimida, N-cloroftalimida e semelhantes a 20 °C até 100 °C, de um modo preferido 50 °C até 60 °C na presença de uma quantidade catalítica de uma base tais como piridina, 4-dimetilaminopiridina e semelhantes, subsequentemente, adicionando um composto representado pela fórmula: R^1-CH= CH_2 em que R^1 é como definido em (1), e uma base tais como trietilamina, di(isopropil)etilamina e semelhantes, e fazendo-os a 0 °C até 100 °C, de um modo preferido 10 °C até 30 °C.

Método D

Fórmula química 28



em que R^1, R^2, R^5, R^6 e R^7 são como definidos em (1)

Passo 1

O primeiro passo é um passo de reacção do composto (iv) obtido no Método A com um reagente representado pela fórmula: R^2MgHal^4 ou R^2Li em que Hal^4 é halogéneo; R^2 é como definido em (1) para obter um composto (vi).

O composto (vi) pode ser obtido fazendo reagir o composto (iv) e o reagente representado pela fórmula: R^2MgHal^4 ou R^2Li em que Hal^4 é halogéneo; R^2 é como definido em (1) a -100 °C até 50 °C, de um modo preferido -78 °C até 10 °C num solvente tais

como tetra-hidrofurano, éter dietílico, tolueno, n-hexano e semelhantes.

Passo 2

O segundo passo é um passo de oxidação do composto (vi) para sintetizar um composto (vii).

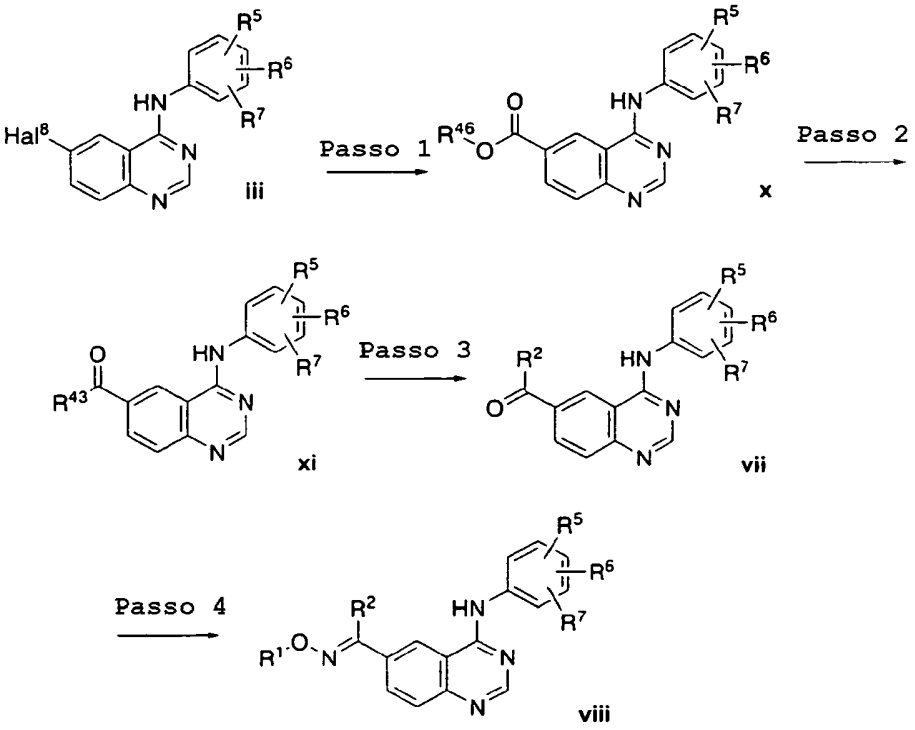
O composto (vii) pode ser obtido oxidando o composto (vi) por um método geral de oxidação de um álcool secundário descrito em Experimental Chemistry Course, vol.23, Quarta edição (editado pela The Chemical Society of Japan) ou semelhantes.

Passo 3

De acordo com o mesmo método que o terceiro passo do Método A, um composto (viii) pode ser obtido a partir do composto (vii).

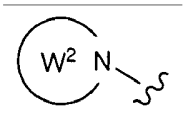
Método E

Fórmula química 29



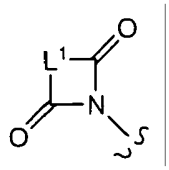
em que Hal^8 é halogéneo; R^{43} é um grupo representado pela fórmula: $R^{44}(R^{45}O)N$ em que R^{44} e R^{45} são independentemente alquilo C1-C3 ou um grupo representado pela fórmula:

Fórmula química 30



em que W^2 é um grupo heterocíclico não aromático contendo azoto; R^{46} é alquilo C1-C3 ou um grupo representado pela fórmula:

Fórmula química 31



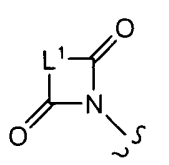
em que L^1 é alquileno C2-C3;

R^1, R^2, R^5, R^6, e R^7 são como definidos em (1)

Passo 1

O primeiro passo é um passo de obtenção de um composto (x) fazendo reagir o composto (iii) obtido no método A com um álcool ou um reagente representado pela fórmula:

Fórmula química 32



em que L^1 é alquileno C2-C3 enquanto é inserido monóxido de carbono na presença de um catalisador de paládio.

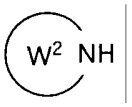
O composto (x) pode ser obtido fazendo reagir o composto (iii) com um álcool tais como metanol, etanol, n-propanol, isopropanol e semelhantes, ou um reagente tal como imida do ácido N-hidroxissuccínico e semelhantes a 50 °C até 150 °C, de um modo preferido 70 °C até 90 °C sob atmosfera de

monóxido de carbono num solvente tais como N,N-dimetilformamida, N,N-dimetilacetamida, N,N'-dimetilimidazolidinona, dimetilsulfóxido e semelhantes na presença de um catalisador de paládio tais como diclorobis(trifenilfosfina)paládio, tetraquis(trifenilfosfina)-paládio, tris(dibenzilidenoacetona)dipaládio, [1,1'-bis(difenilfosfino)ferroceno]dicloropaládio, acetato de paládio+trifenilfosfina, acetato de paládio+1,3-bisdifenilfosfinopropano e semelhantes, e uma base tais como trietilamina, di(isopropil)etilamina e semelhantes.

Passo 2

O segundo passo é um passo de obtenção de um composto (xi) fazendo reagir o composto (x) com um reagente representado pela fórmula: $R^{44}(R^{45}O)NH$ em que R^{44} e R^{45} são independentemente alquilo C1-C3 ou um reagente representado pela fórmula:

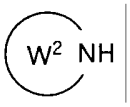
Fórmula química 33



em que W^2 é um grupo heterocíclico não aromático contendo azoto.

O composto (xi) pode ser obtido misturando o composto (x) com um reagente representado pela fórmula: $R^{44}(R^{45}O)NH$ em que R^{44} e R^{45} são independentemente alquilo C1-C3 ou um reagente representado pela fórmula:

Fórmula química 34



em que W^2 é um grupo heterocíclico não aromático contendo azoto num solvente tais como tetra-hidrofurano, N,N-dimetilformamida, clorofórmio, diclorometano e semelhantes, e adicionando um reagente tais como cloreto de metilmagnésio, brometo de metilmagnésio, cloreto de isopropilmagnésio, metil-lítio e semelhantes a -100 °C até 50 °C, de um modo preferido -78 °C até 20 °C para os fazer reagir.

Passo 3

O terceiro passo é um passo de reacção do composto (xi) com um reagente representado pela fórmula: R^2M em que M é Li, Na, K, ou um grupo representado pela fórmula: $MgHal^5$ em que Hal^5 é halogéneo; R^2 é como definido em (1) para obter um composto (vii).

O composto (vii) pode ser obtido fazendo reagir o composto (xi) com um reagente representado pela fórmula: R^2M em que M é Li, Na, K, ou um grupo representado pela fórmula: $MgHal^5$ em que Hal^5 é halogéneo; R^2 é como definido em (1) a -100 °C até 50 °C, de um modo preferido -78 °C até 20 °C num solvente tais como tetra-hidrofurano, éter dietílico, tolueno, n-hexano e semelhantes.

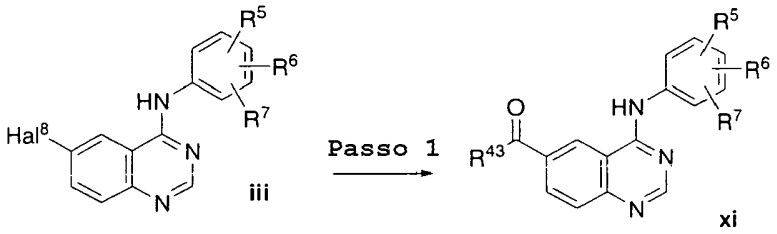
Passo 4

De acordo com o mesmo modo que no terceiro passo do Método A, um composto (viii) pode ser obtido a partir do composto (vii).

Como um método alternativo para o primeiro passo e o segundo passo do Método E, há o seguinte Método E'.

Método E'

Fórmula química 35



em que Hal^8 e R^{43} são como definidos acima; R^5, R^6 e R^7 são como definidos em (1).

Passo 1

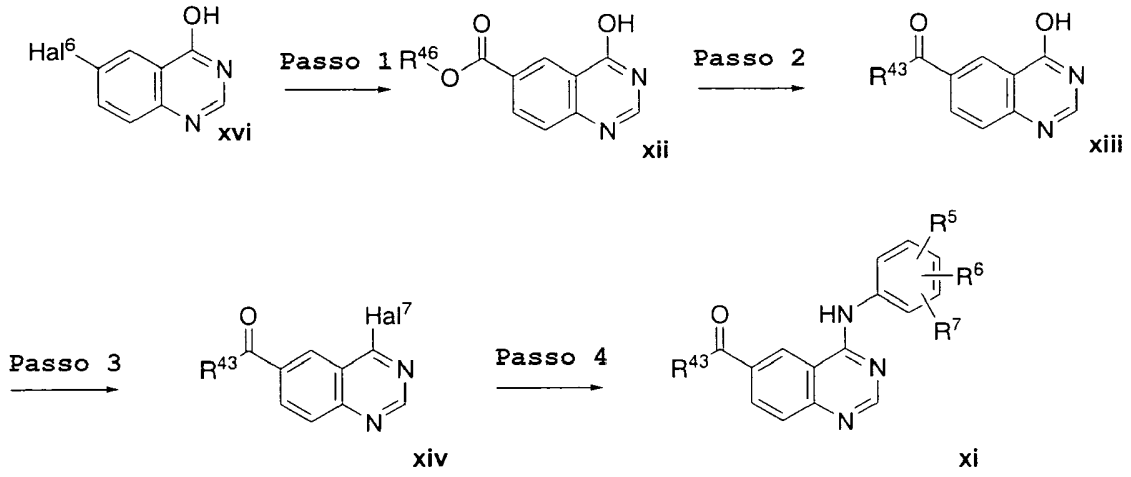
O primeiro passo é um passo de obtenção de um composto (xi) fazendo reagir o composto (iii) com um reagente representado pela fórmula: $R^{43}H$ em que R^{43} é como definido acima, enquanto é inserido monóxido de carbono na presença de um catalisador de paládio.

Ao fazer reagir um reagente representado por $R^{43}H$ em que R^{43} é como definido acima em vez de um álcool ou semelhantes, de acordo com o mesmo modo que o do primeiro passo do Método E, pode ser obtido o composto (xi) a partir do composto (iii).

Como outro método de obtenção de um derivado de amida (xi) do método E, há o seguinte Método E".

Método E"

Fórmula química 36



em que Hal^6 é halogéneo; Hal^7 é halogéneo; R^{43} e R^{46} são como definidos acima; R^5, R^6 e R^7 são como definidos em (1).

Passo 1

De acordo com o mesmo modo que o do primeiro passo do Método E, pode ser obtido um composto (xii) a partir de um composto (xvi).

Passo 2

De acordo com o mesmo modo que o do segundo passo do Método E, pode ser obtido um composto (xiii) a partir do composto (xii).

Passo 3

O terceiro passo é um passo de conversão de um grupo hidroxilo do composto (xiii) em halogéneo para obter um composto (xiv).

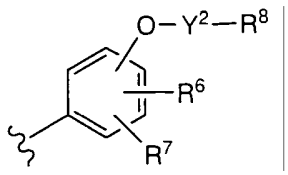
O composto (xiv) pode ser obtido fazendo reagir o composto (xiii) com um agente de halogenação tais como oxicloreto de fósforo, oxibrometo de fósforo e semelhantes a 0 °C até 200 °C, de um modo preferido 20 °C até 150 °C num solvente tais como tolueno, tetra-hidrofurano e semelhantes na presença de uma base tais como trietilamina, diisopropiletilamina, piridina e semelhantes.

Passo 4

De acordo com o mesmo modo que o do primeiro passo do Método A, pode ser obtido um composto (xi) a partir do composto (xiv).

O presente composto (I) no qual A é um grupo representado pela fórmula:

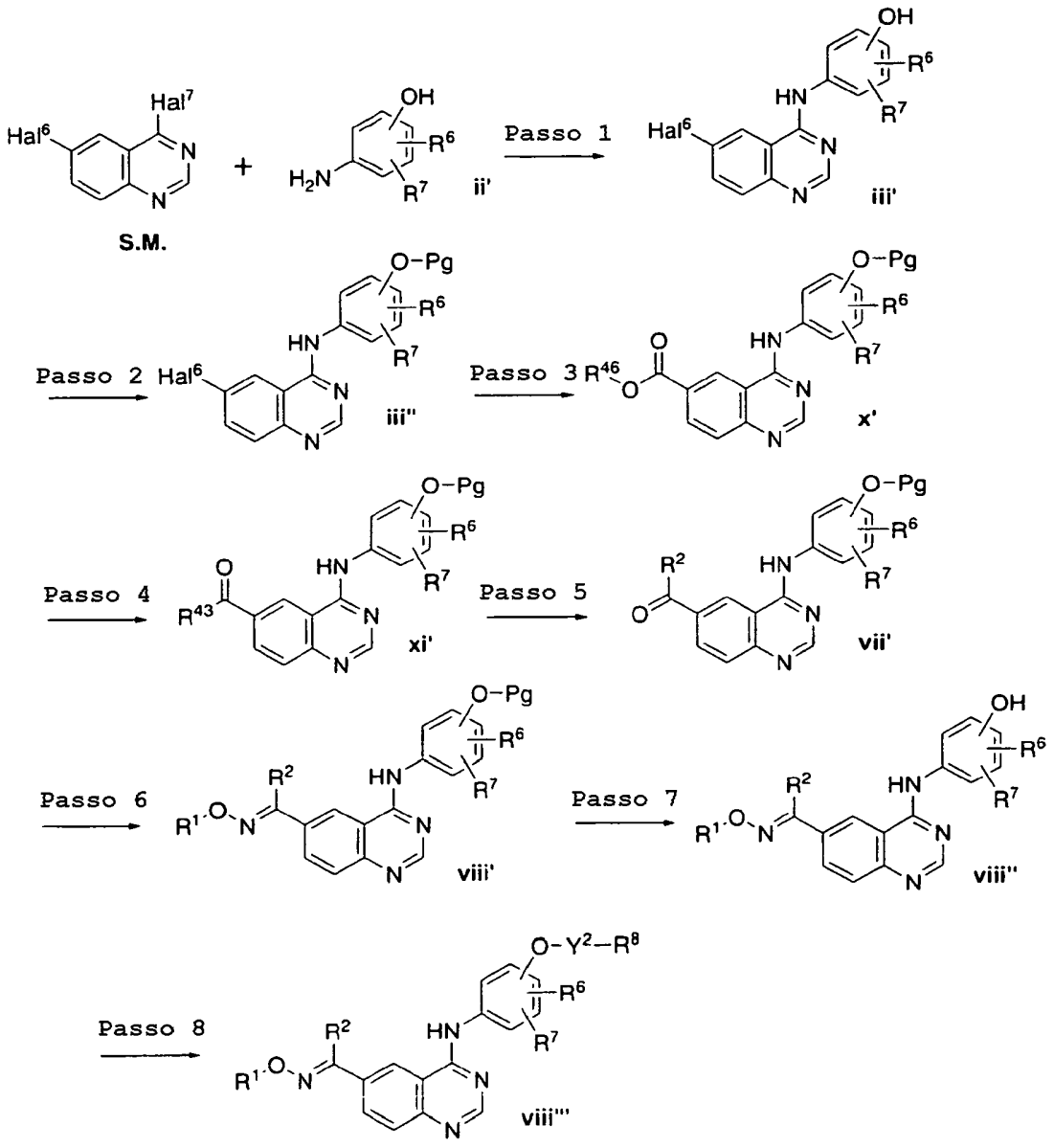
Fórmula química 37



em que Y^2 é uma ligação simples ou alquileno C1-C3; R^6, R^7 e R^8 são como definidos em (1) pode ser também sintetizado pelo Método F seguinte.

Método F

Fórmula Química 38



em que Hal^6 e Hal^7 são halogéneo; Y^2 é uma ligação simples ou alquileno C1-C3; Pg é um grupo de protecção adequado para um grupo hidroxilo; R^1, R^2, R^6, R^7 e R^8 são como definidos em (1); R^{43} e R^{46} são como definidos acima.

Passo 1

De acordo com o mesmo modo que o do primeiro passo do Método A, pode ser obtido um composto (iii') a partir de um composto de partida (M.P.) e um composto (ii').

Passo 2

O segundo passo é um passo de ligação de um grupo de protecção a um grupo hidroxilo do composto (iii') para sintetizar um composto (iii").

Um grupo de protecção adequado pode ser ligado pelo método descrito em Protective Groups in Organic Synthesis, Theodora W Green (John Wiley & Sons) ou semelhantes.

Passo 3

De acordo com o mesmo modo que o do primeiro passo do Método E, pode ser obtido um composto (x') a partir do composto (iii").

Passo 4

De acordo com o mesmo modo que o do segundo passo do Método E, pode ser obtido um composto (xi') a partir do composto (x').

Passo 5

De acordo com o mesmo modo que o do terceiro passo do Método E, pode ser obtido um composto (vii') a partir do composto (xi').

Passo 6

De acordo com o mesmo modo que o do terceiro passo do Método A, pode ser obtido um composto (viii') a partir do composto (vii').

Passo 7

O sétimo passo é um passo de remoção de um grupo de protecção do composto (viii') para sintetizar um composto (viii").

A desprotecção pode ser realizada na condição adequada pelo método descrito em Protective Groups in Organic Synthesis, Theodora W Green (John Wiley & Sons) ou semelhantes.

Passo 8

O oitavo passo é um passo de reacção do composto (viii") com um reagente representado pela fórmula: R^8-Y^2-Hal^8 em que Hal^8 é halogéneo; Y^2 é uma ligação simples ou alquileno C1-C3; R^8 é como definido em (1) para obter um composto (viii"').

O composto (viii"') pode ser obtido fazendo reagir o composto (viii") com um reagente representado pela fórmula: R^8-Y^2-Hal^8 em que Hal^8 é halogéneo; Y^2 é uma ligação simples ou alquileno C1-C3; R^8 é como definido em (1) a -20 °C até 200 °C, de um modo preferido 0 °C até 100 °C num solvente tais como N,N-dimetilformamida, dimetilsulfóxido, tetra-hidrofurano, éter dietílico, tolueno, n-hexano e semelhantes na presença de uma base tais como carbonato de césio, carbonato de potássio, carbonato de sódio, carbonato de lítio, bicarbonato de potássio, bicarbonato de sódio, hidróxido de potássio, hidróxido de sódio, trietilamina, piridina e semelhantes.

Como Y^2 no Método F é preferido alquileno C1-C3. Em particular, é preferido metileno.

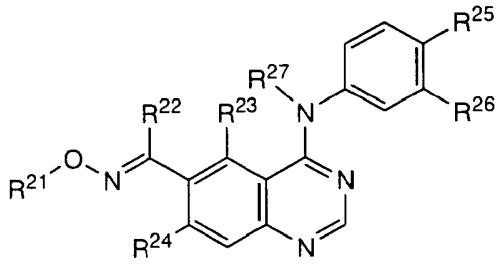
Como R^8 no Método F é preferido fenilo opcionalmente substituído com halogéneo ou piridilo opcionalmente substituído com halogéneo.

Um reagente de alcoxiamina representado pela fórmula: R^1-O-NH_2 em que R^1 é como definido em (1) utilizado no terceiro passo do Método A está comercialmente disponível ou pode ser sintetizado utilizando, como uma matéria-prima de partida, um composto álcool que pode ser sintetizado de acordo com o método descrito em J. Med. Chem., 1999, 42:2007-2020, Liebigs Ann. Chem., 1988:1149-1153, Organic Letters, 2004, 6:4069-4072, Organic Letters, 2005, 7:937-939, documento WO 04/054514 ou semelhantes, de acordo com o método descrito no documento WO 02/062313 ou semelhantes.

No composto representado pela fórmula (I) são preferidos compostos representados pelas fórmula (I-A) a fórmula (I-P) seguintes.

Um composto representado na fórmula (I-A):

Fórmula química 39



(I-A)

em que R^{21} é alquilo substituído com amino opcionalmente substituído com um substituinte seleccionado do grupo substituinte C consistindo de alquilo, alcenilo, alcinilo, arilo opcionalmente substituído, aralquilo, alquiloxilo, hidroxialquilo, hidroxialquiloxialquilo, haloalquilo, aminoalquilo opcionalmente substituído com 1 ou 2 alquilo(s), alquilsulfonilo, alquilsulfonilalquilo, alquilcarbonilo opcionalmente substituído com halogéneo ou alquiloxilo, alquiloxicarbonilo, cicloalquilo opcionalmente substituído, carboxialquilo, aminocarbonilalquilo opcionalmente substituído, aminocarboniloxialquilo opcionalmente substituído, alquiloxialquilo, alquiltioalquilo, alquilcarbonilaminoalquilo, alquilsulfonilaminoalquilo, alquilsulfonil(alquil)aminoalquilo, alquiloxicarbonilalquilo, alquiltio(hidroxi)alquilo, cicloalquilalquilo, cianoalquilo, aminoalquilcarbonilo opcionalmente substituído, heteroarilo opcionalmente substituído, heteroarilalquilo, hidroxialquiloxialquilo, grupo

heterocíclico não aromático opcionalmente substituído e alquilo heterocíclico não aromático opcionalmente substituído;

alquilo substituído com um grupo heterocíclico não aromático contendo azoto, em que o grupo heterocíclico não aromático contendo azoto é seleccionado de pirrolidinilo, piperidilo, piperazinilo, morfolinilo e tiomorfolinilo, opcionalmente substituído com um substituinte seleccionado do grupo substituinte D consistindo de halogéneo; arilo; hidroxilo; oxo; aminocarbonilo opcionalmente substituído; alquiloxicarbonilo; alquilo opcionalmente substituído com um substituinte seleccionado do grupo substituinte H consistindo de aminocarbonilo opcionalmente substituído, ciano, alquiloxilo, alquilsulfonilamino, amino, carboxilo, alquiloxicarbonilo e hidroxilo; alquilaminocarbonilo; carboxilo; ciano, alquilsulfonilo; alquilcarbonilo; alcenilcarbonilo; alquilsulfonilalquilcarbonilo; alquiloxialquilcarbonilo; alquilcarbonilamino; aminocarboniloxilo; um grupo heterocíclico não aromático contendo azoto; e carbonilo heterocíclico não aromático; ou

um grupo heterocíclico não aromático contendo azoto, em que o grupo heterocíclico não aromático contendo azoto é seleccionado de azetidinilo, pirrolidinilo e piperidilo, opcionalmente substituído com um substituinte seleccionado do grupo substituinte B consistindo de alquiloxicarbonilo, aminocarbonilo opcionalmente substituído, oxo, amino, carboxilo, ciano, cianoalquilo, hidroxialquilo, alquilcarbonilamino, alquilsulfonilamino e aminocarbonilalquilo;

R^{22} é alquilo opcionalmente substituído com um substituinte seleccionado do grupo substituinte K consistindo de amino opcionalmente substituído com alquilo, hidroxilo, alquiloxilo e halogéneo; alcenilo opcionalmente substituído com um substituinte seleccionado do grupo substituinte K, alcinilo opcionalmente substituído com um substituinte seleccionado do grupo substituinte K; hidroxilo; halogéneo; fenilo; piridilo; furilo; tienilo; ou tiazolilo;

um de R^{23} e R^{24} é um átomo de hidrogénio e o outro é um átomo de hidrogénio, alquiloxilo, alquiloxialquiloxilo, halogéneo ou aminoalquilo opcionalmente substituído com alquilo;

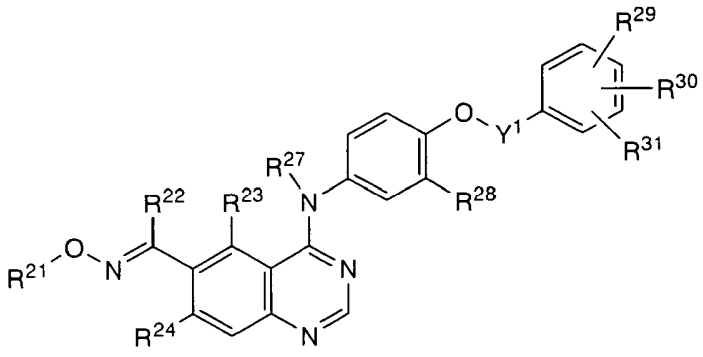
R^{27} é um átomo de hidrogénio, alquilo ou acilo; e

R^{25} e R^{26} são, cada, independentemente um átomo de hidrogénio, halogéneo, alcinilo, hidroxilo, alquiloxilo, alceniloxilo, alciniloxilo ou heteroarilalquiloxilo,

um seu sal farmaceuticamente aceitável ou um seu solvato.

Um composto representado pela fórmula (I-B):

Fórmula química 40



(I-B)

em que R^{21}, R^{22}, R^{23}, R^{24} e R^{27} são como definidos acima;

Y^1 é alquileno C1-C3;

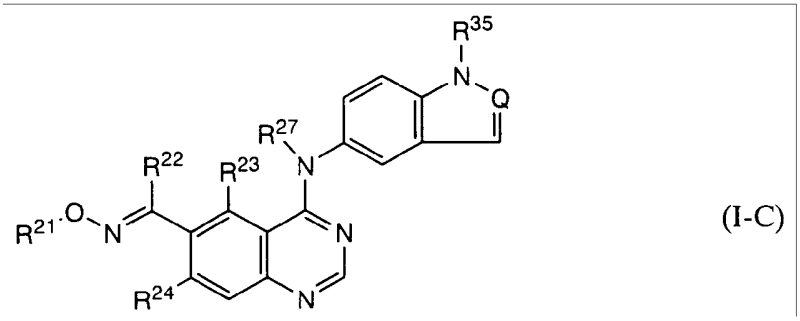
R^{28} é alquilo, alquiloxilo, alcinilo ou halogéneo; e

R^{29}, R^{30} e R^{31} são, cada, independentemente um átomo de hidrogénio ou um substituinte seleccionado do grupo substituinte F consistindo de halogéneo, carboxilo, alquilo, haloalquilo, hidroxialquilo, alquiloxilo, alquiloxicarbonilo e amino opcionalmente substituído,

um seu sal farmaceuticamente aceitável ou um seu solvato.

Um composto representado pela fórmula (I-C):

Fórmula química 41



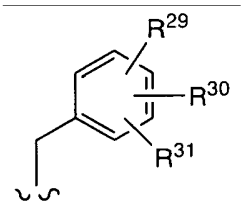
(I-C)

em que R^{21}, R^{22}, R^{23}, R^{24} e R^{27} são como definidos acima;

R^{35} é alquilo opcionalmente substituído com um substituinte seleccionado do grupo substituinte L consistindo de hidroxilo, alquiloxilo, halogéneo e ciano; alcenilo opcionalmente substituído com um substituinte seleccionado do grupo

substituinte L; alcinilo opcionalmente substituído com um substituinte seleccionado do grupo substituinte L; ou um grupo representado pela fórmula:

Fórmula química 42

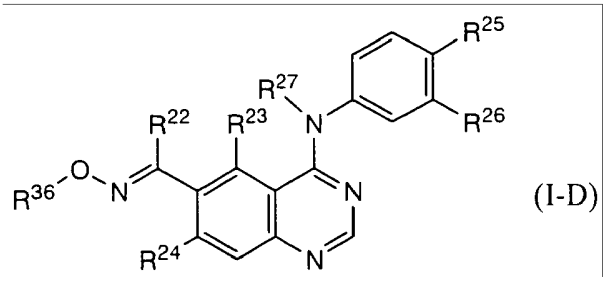


em que R^{29}, R^{30} e R^{31} são como definidos acima;

Q é N ou CH_2, um seu sal farmaceuticamente aceitável ou um seu solvato.

Um composto representado pela fórmula (I-D):

Fórmula química 43



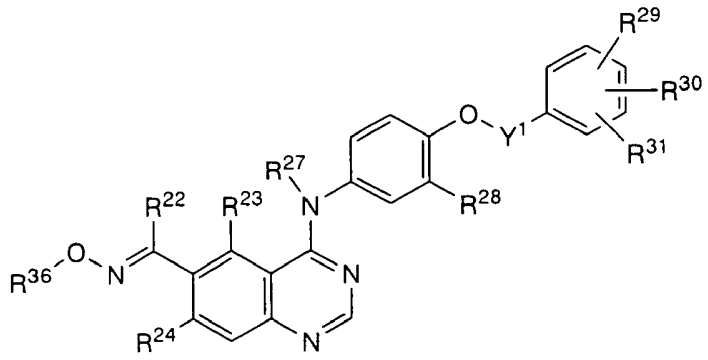
em que R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26} e R^{27} são como definidos acima; e R^{36} é alquilo substituído com aminocarbonilo opcionalmente substituído com um substituinte seleccionado do grupo substituinte C ou

alquilo substituído com carbonilo heterocíclico não aromático, em que o heterociclo não aromático contendo azoto é seleccionado de pirrolidinilo, piperidinilo, piperazinilo, morfolinilo e tiomorfolinilo, opcionalmente substituído com um substituinte seleccionado do grupo substituinte D,

um seu sal farmaceuticamente aceitável ou um seu solvato.

Um composto representado pela fórmula (I-E):

Fórmula química 44



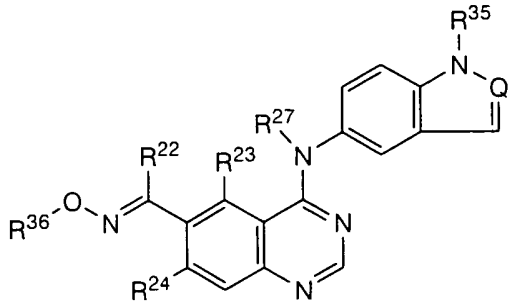
(I-E)

em que R^{21}, R^{22}, R^{23}, R^{24}, R^{27}, R^{28}, R^{29}, R^{30}, R^{31}, R^{36} e Y^1 são como definidos acima,

um seu sal farmaceuticamente aceitável ou um seu solvato.

Um composto representado pela fórmula (I-F):

Fórmula química 45



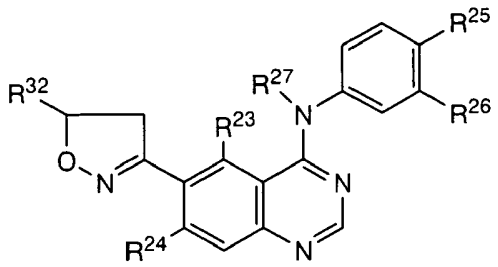
(I-F)

em que R^{22}, R^{23}, R^{24} R^{27}, R^{36} e Q são como definidos acima,

um seu sal farmaceuticamente aceitável ou um seu solvato.

Um composto representado pela fórmula (I-G):

Fórmula química 46



(I-G)

em que R^{23}, R^{24}, R^{25}, R^{26} e R^{27} são como definidos acima;

R^{32} é alquilo substituído com amino opcionalmente substituído com um substituinte seleccionado do grupo substituinte C,

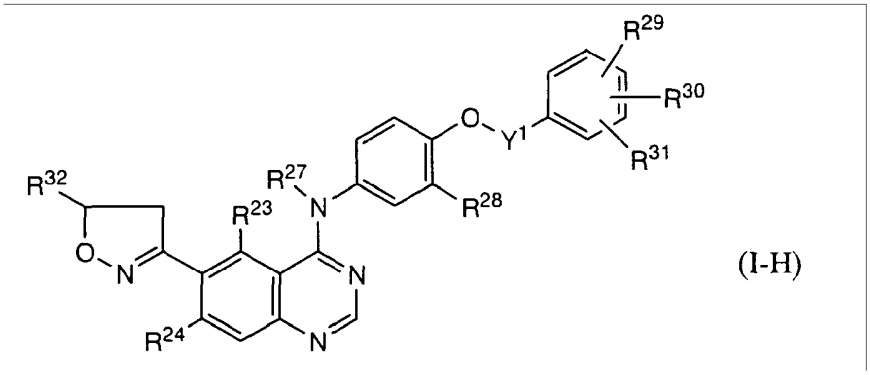
alquilo substituído com um grupo heterocíclico não aromático contendo azoto, em que o grupo heterocíclico não aromático contendo azoto é seleccionado de pirrolidinilo, piperidilo,

piperazinilo, morfolinilo e tiomorfolinilo, opcionalmente substituído com um substituinte seleccionado do grupo substituinte D, ou um grupo heterocíclico não aromático contendo azoto, em que o grupo heterocíclico não aromático contendo azoto é seleccionado de azetidinilo, pirrodilinilo e piperidilo, opcionalmente substituído com um substituinte seleccionado do grupo substituinte B,

um seu sal farmaceuticamente aceitável ou um seu solvato.

Um composto representado pela fórmula (I-H):

Fórmula química 47



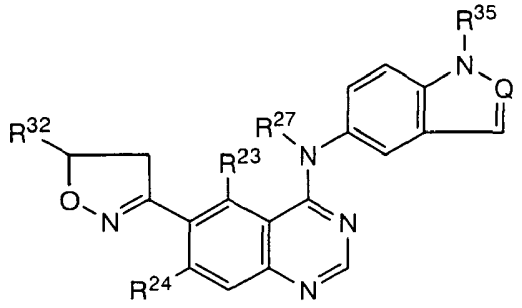
(I-H)

em que R^{23}, R^{24}, R^{27}, R^{28}, R^{29}, R^{30}, R^{31}, R^{32} e Y^1 são como definidos acima,

um seu sal farmaceuticamente aceitável ou um seu solvato.

Um composto representado pela fórmula (I-I):

Fórmula química 48



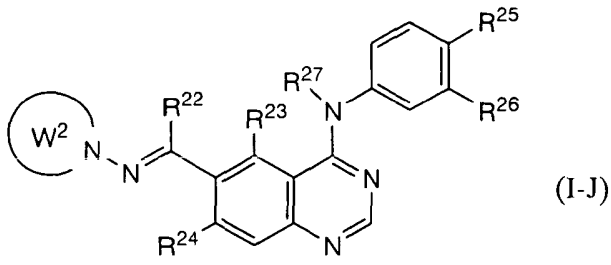
(I-I)

em que R^{23}, R^{24}, R^{27}, R^{32}, R^{35}, e Q são como definidos acima,

um seu sal farmaceuticamente aceitável ou um seu solvato.

Um composto representado pela fórmula (I-J):

Fórmula química 49



(I-J)

em que R^{22}, R^{23}, R^{24}, R^{25}, R^{26} e R^{27} são como definidos acima;

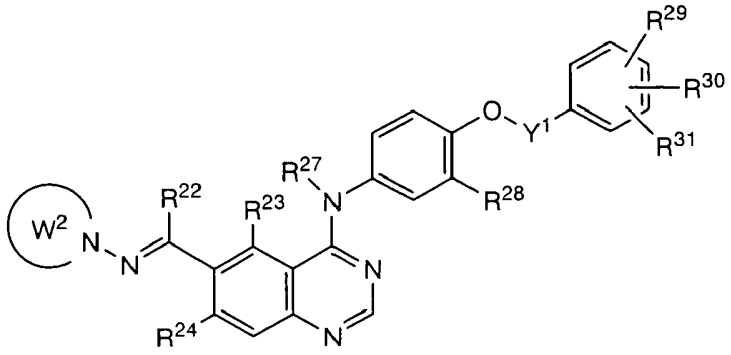
W^2 é pirrolidinilo opcionalmente substituído com um substituinte seleccionado do grupo substituinte J, piperidilo opcionalmente substituído com um substituinte seleccionado do grupo substituinte J, piperazinilo opcionalmente substituído com um substituinte seleccionado do grupo substituinte J, morfolinilo opcionalmente substituído com um substituinte seleccionado do

grupo substituinte J ou triazolilo opcionalmente substituído com um substituinte seleccionado do grupo substituinte J,

um seu sal farmaceuticamente aceitável ou um seu solvato.

Um composto representado pela fórmula (I-K):

Fórmula química 50



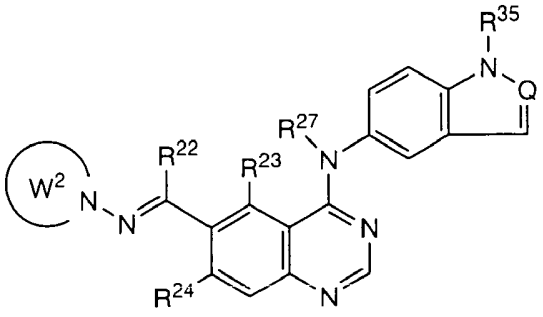
(I-K)

em que R^{22}, R^{23}, R^{24}, R^{27}, R^{28}, R^{29}, R^{30}, R^{31}, Y^1 e W^2 são como definidos acima,

um seu sal farmaceuticamente aceitável ou um seu solvato.

Um composto representado pela fórmula (I-L):

Fórmula química 51



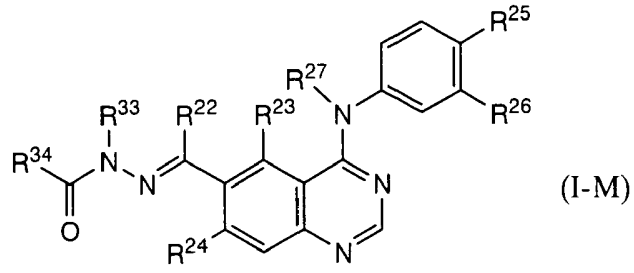
(I-L)

em que R^{22}, R^{23}, R^{24}, R^{27}, R^{35} W^2 e Q são como definidos acima,

um seu sal farmaceuticamente aceitável ou um seu solvato.

Um composto representado pela fórmula (I-M):

Fórmula química 52



(I-M)

em que R^{22}, R^{23}, R^{24} R^{25}, R^{26} e R^{27} são como definidos acima;

R^{33} é um átomo de hidrogénio, alquilo C1-C6 opcionalmente substituído com um substituinte seleccionado do grupo substituinte L, alcenilo C2-C6 opcionalmente substituído com um substituinte seleccionado do grupo substituinte L ou alcinilo C2-C6 opcionalmente substituído com um substituinte seleccionado do grupo substituinte L; e

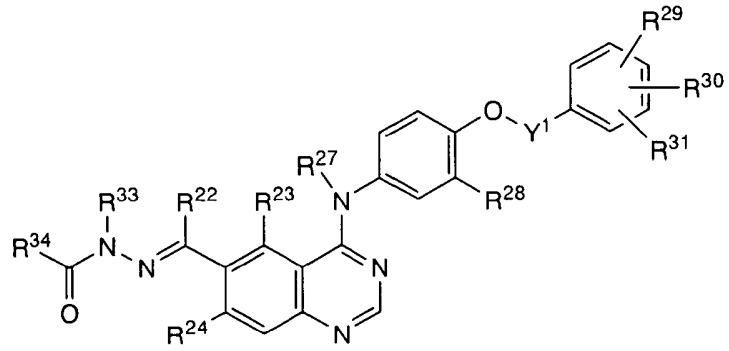
R^{34} é alquilo substituído com amino opcionalmente substituído com um substituinte seleccionado do grupo substituinte C, alquilo substituído com um grupo heterocíclico não aromático contendo azoto opcionalmente substituído com um substituinte seleccionado do grupo substituinte D, arilo opcionalmente substituído com um substituinte seleccionado do grupo substituinte F, heteroarilo opcionalmente substituído com um substituinte seleccionado do grupo substituinte F ou um grupo heterocíclico não aromático

opcionalmente substituído com um substituinte seleccionado do grupo substituinte F,

um seu sal farmaceuticamente aceitável ou um seu solvato.

Um composto representado pela fórmula (I-N):

Fórmula química 53



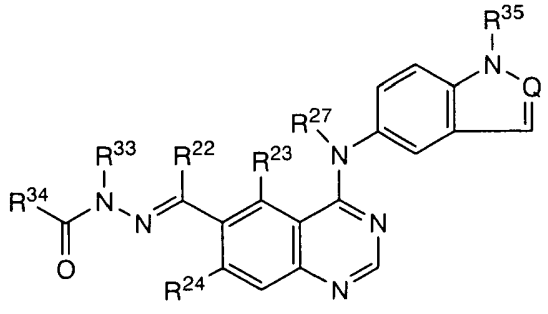
(I-N)

em que R^{22}, R^{23}, R^{24}, R^{27}, R^{28}, R^{29}, R^{30}, R^{31}, R^{33}, R^{34} e Y^1 são como definidos acima,

um seu sal farmaceuticamente aceitável ou um seu solvato.

Um composto representado pela fórmula (I-O):

Fórmula química 54



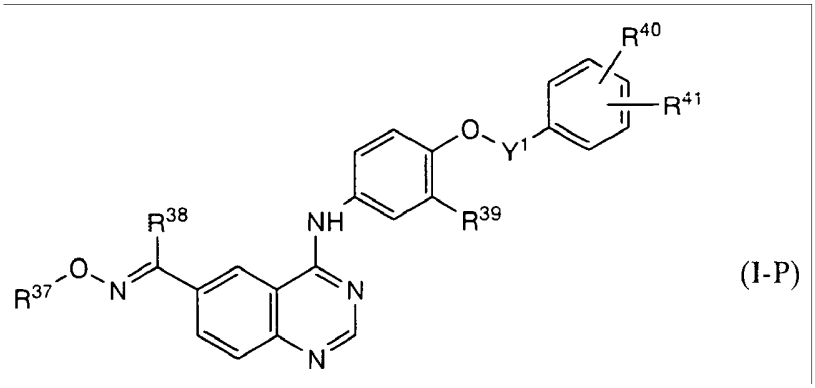
(I-O)

em que R^{22}, R^{23}, R^{24} R^{27}, R^{34}, R^{35} e Q são como definidos acima,

um seu sal farmaceuticamente aceitável ou um seu solvato.

Um composto representado pela fórmula (I-P):

Fórmula química 55



(I-P)

em que R^{37} é alquilo substituído com amino opcionalmente substituído com alquilo, hidroxialquilo, alquilcarbonilaminoalquilo ou um grupo heterocíclico não aromático; alquilo substituído com um grupo heterocíclico não aromático contendo azoto opcionalmente substituído com alquilo, hidroxialquilo ou alquilcarbonilamino; ou

um grupo heterocíclico não aromático contendo azoto substituído com hidroxialquilo;

R^{38} é alcinilo C2-C4;

R^{39} é halogéneo;

R^{40} é um grupo representado pela fórmula: $-Y^3-R^{42}$ em que Y^3 é alquileno, o qual pode estar intervalado com -O-;

R^{42} é fenilo opcionalmente substituído com halogéneo ou piridilo opcionalmente substituído com halogéneo;

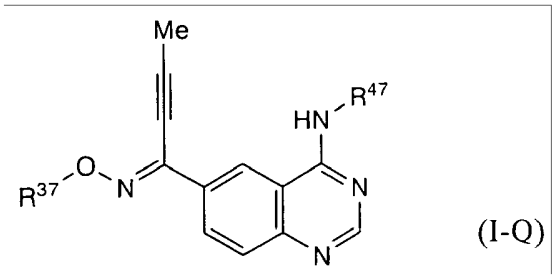
R^{41} é halogéneo;

Y^1 é como definido acima,

um seu sal farmaceuticamente aceitável ou um seu solvato.

Um composto representado pela fórmula (I-Q):

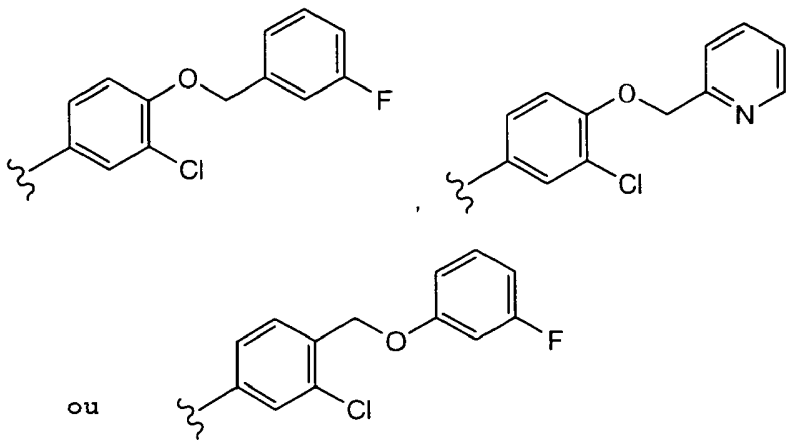
Fórmula química 56



(I-Q)

em que R^{47} é um grupo representado pela fórmula:

Fórmula química 57



R^{37} é como definido acima,

um seu sal farmaceuticamente aceitável ou um seu solvato.

Como R^{22} nos compostos representados pela fórmula (I-A) até à fórmula (I-F) e pela fórmula (I-J) até à fórmula (I-O) é preferido metilo, etilo, n-propilo, isopropilo, propinilo, butinilo ou fenilo.

Aqui, o "solvato" inclui, por exemplo, um solvato com um solvente orgânico, um hidrato e semelhantes. Quando se forma um solvato, o composto pode estar coordenado com um número arbitrário de moléculas de água.

Quando se refere ao "presente composto" estão também incluídos um sal farmaceuticamente aceitável e um seu hidrato. Os exemplos incluem sais de metais alcalinos (lítio, sódio, potássio etc.), ou metais alcalino-terrosos (magnésio, cálcio etc.), e amónio, bases orgânicas e aminoácidos, e sais com

ácidos inorgânicos (ácido clorídrico, ácido bromídrico, ácido fosfórico, ácido sulfúrico etc.), ou ácidos orgânicos (ácido acético, ácido cítrico, ácido maleico, ácido fumárico, ácido benzenossulfónico, ácido p-toluenossulfónico etc.). Estes sais podem ser preparados por métodos que são geralmente utilizados.

Além disso, o presente composto não está limitado aos isómeros especificados, mas inclui todos os isómeros e racematos possíveis.

O presente composto, como descrito nos Exemplos Experimentais descritos mais à frente, exibe uma excelente actividade de inibição da proliferação celular e pode ser utilizado como uma "composição farmacêutica útil para o tratamento de cancro" e uma "terapêutica para um cancro".

Quando o presente composto é administrado a um humano com o objectivo de tratar as doenças supramencionadas, este pode ser administrado por via oral como pós, granulados, comprimidos, cápsulas, pílulas, soluções ou semelhantes, ou administrado por via parentérica como injectáveis, supositórios, agentes de absorção transdérmica, inalantes ou semelhantes. E, uma quantidade eficaz do presente composto é misturada, se for necessário, com aditivos farmacêuticos tais como excipientes, aglutinantes, humectantes, desintegrantes, lubrificantes e semelhantes que são adequados para uma forma de dosagem pelo que, desse modo, o presente composto pode ser formulado em preparações farmacêuticas. No caso de injectáveis, o presente composto, em conjunto com um veículo adequado, é submetido a tratamento de esterilização para obter preparações.

A dose é diferente dependendo do estado de uma doença, da via de administração, e da idade ou peso de um doente e é, habitualmente, de 0,1 a 100 mg/kg/dia, de um modo preferido 1 a 20 mg/kg/dia quando administrado por via oral a um adulto.

Os seguintes Exemplos e Exemplos de Ensaio ilustram a presente invenção em mais pormenor abaixo, mas a presente invenção não é limitado pelos mesmos.

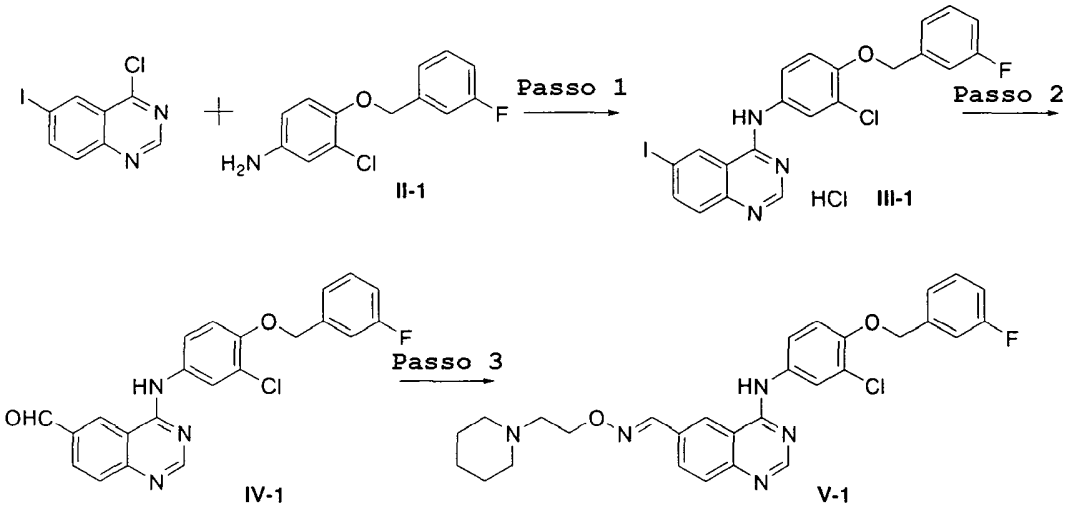
Nos exemplos são utilizadas as seguintes abreviaturas.

Me: metilo
Et: etilo
nPr: n-propilo
iPr: isopropilo
Ph: fenilo

Exemplos

Exemplo 1

Fórmula química 58



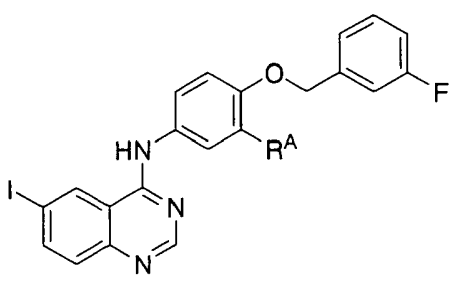
Passo 1 Síntese de cloridrato de 4-(3-cloro-4-(3-fluorobenziloxi)fenilamino)-6-iodoquinazolina (III-1)

Em 180 mL de tetra-hidrofurano foram dissolvidos 4-cloro-6-iodoquinazolina (6,0 g) e 3-cloro-4-(3-fluorobenziloxi)anilina (II-1, 5,2 g), seguida de aquecimento a refluxo durante 3 horas. Foi filtrado um precipitado e lavado com tetra-hidrofurano para obter cloridrato de 4-(4-(3-fluorobenziloxi)fenilamino)-6-iodoquinazolina (III-1, 10,5 g) como um sólido amarelo.

RMN de ^1H (d_6-DMSO, δ): 11,47 (1H, s l), 9,25 (1H, s), 8,94 (1H, s), 8,36 (1H, dd, J = 1,8 Hz, J = 8,7 Hz), 7,92 (1H, d, J = 2,7 Hz), 7,71 (1H, d, J = 8,7 Hz), 7,66 (1H, dd, J = 2,7 Hz, J = 8,7 Hz), 7,48 (1H, dt, J = 6,0 Hz, J = 7,8 Hz), 7,37-7,30 (3H, m), 7,19 (1H, dt, J = 2,7 Hz, J = 8,7 Hz), 5,30 (2H, s).

O composto seguinte foi sintetizado de acordo com o mesmo método que o do primeiro passo acima.

Fórmula química 59



(III)

Quadro 1

Nº do Composto	R^A	RMN de ^1H (d_6-DMSO)
III-2	-F	9,86(1H, s), 8,95(1H, d, J = 1,5 Hz), 8,61(1H, s), 8,11(1H, dd, J = 1,8 Hz, J = 8,7 Hz), 7,89(1H, J = 2,4 Hz, J = 13,5 Hz), 7,60-7,49(2H, m), 7,45(1H, dd, J = 6,3 Hz, J = 8,1 Hz), 7,36-7,23(3H, m), 7,19(1H, dt, J = 8,4 Hz, J = 2,1 Hz), 5,22(2H, s).
III-3	-OMe	11,26(1H, s l), 9,18(1H, s), 8,89(1H, s), 8,34(1H, dd, J = 1,5 Hz, J = 8,7 Hz), 7,66(1H, d, J = 8,7 Hz), 7,46(1H, dt, J = 6,3 Hz, J = 8,1 Hz), 7,39(1H, d, J = 2,1 Hz), 7,34-7,25(3H, m), 7,22-7,13(1H, m), 7,13(1H, d, J = 8,7 Hz), 5,17(2H, s), 3,82(3H, s).

Passo 2 Síntese de 4-(3-cloro-4-(3-fluorobenziloxi)fenilamino)-6-formilquinazolina (IV-1)

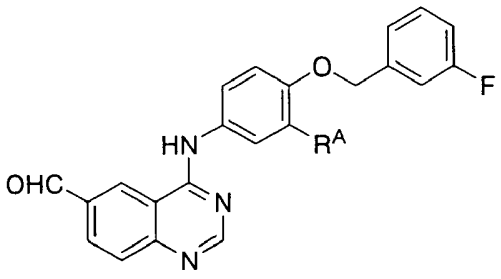
Em 100 mL de dimetilformamida foi dissolvido cloridrato de 4-(4-(3-fluorobenziloxi)fenilamino)-6-iodoquinazolina (III-1, 5,0 g) e foram adicionadas 1,25 g de formato de sódio, diclorobis(trifenilfosfina)paládio (324 mg) e trietilamina

(3,2 mL). A mistura reaccional foi desgaseificada e agitada sob aquecimento a 80 °C durante 3 horas sob atmosfera de monóxido de carbono. Depois disso, a mistura reaccional foi vertida para água gelada e extraída com acetato de etilo. O extracto foi lavado com água e solução de cloreto de sódio, e seco com sulfato de magnésio. A solução seca foi filtrada com Celite, concentrada e pulverizada com um acetato de etilo-hexano (1:2) para obter 4-(4-(3-fluorobenziloxi)fenilamino)-6-formilquinazolina (IV-1, 2,86 g) como um sólido amarelo.

RMN de ^{1}H (d_6-DMSO, δ): 10,24 (1H, s), 10,13 (1H, s), 9,16 (1H, s), 8,6 9(1H, s), 8,27 (1H, d l, J = 8,7 Hz), 8,03 (1H, d, J = 2,1 Hz), 7,90 (1H, d, J = 9,0 Hz), 7,74 (1H, dd, J = 2,7 Hz, J = 8,7 Hz), 7,48 (1H, dt, J = 6,0 Hz, J = 8,4 Hz), 7,36-7,30 (2H, m), 7,30 (1H, d, J = 8,7 Hz), 7,19 (1H, t l, J = 8,7 Hz), 5,27 (2H, s).

O composto seguinte foi sintetizado de acordo com o mesmo método que o do segundo passo acima.

Fórmula química 60



(IV)

Quadro 2

Nº do Composto	R^A	RMN de ^1H (d_6-DMSO)
IV-2	-F	10,24(1H, s), 10,14(1H, s), 9,16(1H, s), 8,69(1H, s), 8,26(1H, dd, J = 1,5 Hz, J = 8,7 Hz), 7,94-7,85(2H, m), 7,55(1H, d l, J = 9,0 Hz), 7,47(1H, dt, J = 6,3 Hz, J = 8,1 Hz), 7,36-7,26(3H, m), 7,23-7,15(1H, m), 5,23(2H, s).
IV-3	-OMe	10,13(2H, s), 9,18(1H, s), 8,64(1H, s), 8,25(1H, dd, J = 1,5 Hz, J = 8,7 Hz), 7,88(1H, d, J = 8,4 Hz), 7,52-7,38(3H, m), 7,34-7,26(2H, m), 7,22-7,12(1H, m), 7,07(1H, d, J = 8,7 Hz), 5,14(2H, s), 3,83(3H, s).

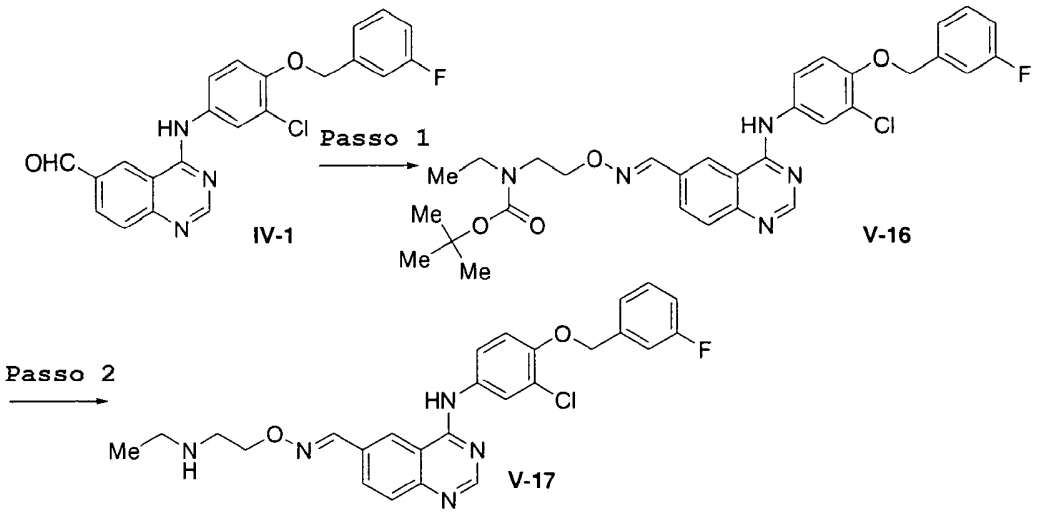
Passo 3 Síntese de 4-(3-cloro-4-(3-fluorobenziloxi)-fenilamino)-6-(2-(1-piperidil)etoxiimino)quinazolina (V-1)

Numa mistura de tetra-hidrofurano (2 mL) e água (0,1 mL) foram dissolvidos 4-(3-cloro-4-(3-fluorobenziloxi)fenilamino)-6-formilquinazolina (IV-1, 50 mg) e 2-(1-piperidil)etoxiamina dicloridrato (36,5 mg), e a mistura foi agitada à temperatura ambiente de um dia para o outro. A mistura reaccional foi diluída com acetato de etilo, lavada sequencialmente com solução aquosa saturada de bicarbonato de sódio e solução aquosa de cloreto de sódio, e seca sobre sulfato de magnésio. Após concentração, o resíduo foi purificado por cromatografia (eluindo com hexano: acetato de etilo = 2:3) utilizando uma coluna amino, e ainda repurificado por cromatografia em camada fina para obter 4-(3-cloro-4-(3-fluorobenziloxi)fenilamino)-6-(2-(1-piperidil)etoxiimino)quinazolina (V-1, 13 mg).

RMN de ^{1}H (d_6-DMSO, δ): 9,95 (1H, s), 8,63 (1H, s), 8,59 (1H, s), 8,34 (1H, s), 8,10 (1H, d, J = 9,3 Hz), 8,00 (1H, d, J = 2,4 Hz), 7,79 (1H, d, J = 8,7 Hz), 7,72 (1H, dd, J = 9,0 Hz, J = 2,1 Hz), 7,51-7,44 (1H, m), 7,36-7,31 (2H, m), 7,28 (1H, d, J = 9,0 Hz), 7,19 (1H, t l, J = 9,0 Hz), 5,26 (2H, s), 4,28 (2H, t, J = 6,0 Hz), 2,63 (2H, t, J = 6,0 Hz), 2,41 (4H, t, J = 4,8 Hz), 1,50 (4H, quin, J = 5,3 Hz), 1,45-1,35 (2H, m).

Exemplo 2

Fórmula química 61



Passo 1 Síntese de 4-(3-cloro-4-(3-fluorobenziloxi)fenilamino)-6-(2-(N-(t-butoxicarbonil)-N-etilamino)etiloxiimino)quinazolina (V-16)

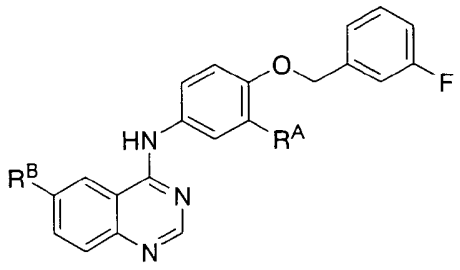
Em tetra-hidrofurano (1,5 mL) foram dissolvidos 4-(3-cloro-4-(3-fluorobenziloxi)fenilamino)-6-formilquinazolina (IV-1, 120 mg) e N-(t-butoxicarbonil)etilaminoetoxiamina (110 mg), e

foram adicionados 134 µL de ácido clorídrico 2 mol/L, em seguida a mistura foi agitada à temperatura ambiente durante 4 horas. Depois de a reacção estar completa, a mistura reaccional foi vertida para solução aquosa saturada de bicarbonato de sódio gelada e extraída com acetato de etilo. A camada orgânica foi lavada com água e solução aquosa de cloreto de sódio, seca sobre sulfato de magnésio e concentrada. O resíduo resultante foi purificado por cromatografia em coluna amino (eluindo com hexano: acetato de etilo = 1:1) e ainda repurificado por cromatografia sobre sílica gel (eluindo com hexano: acetato de etilo = 1:1) para obter 4-(3-cloro-4-(3-fluorobenziloxi)-fenilamino)-6-(2-(N-(t-butoxicarbonil)-N-etilamino)etiloxiimino)quinazolina (V-16, 96 mg) como um óleo amarelo viscoso.

RMN de ^{1}H (d_6-DMSO, δ): 9,93 (1H, s), 8,63 (1H, s l), 8,60 (1H, s), 8,34 (1H, s), 8,12 (1H, dd, J = 1,2 Hz, J = 9,0 Hz), 8,01 (1H, d, J = 2,4 Hz), 7,79 (1H, d, J = 8,4 Hz), 7,72 (1H, dd, J = 2,4 Hz, J = 8,4 Hz), 7,48 (1H, dt, J = 6,0 Hz, J = 8,1 Hz), 7,36-7,30 (2H, m), 7,28 (1H, d, J = 9,0 Hz), 7,23-7,14 (1H, m), 5,26 (2H, s), 4,26 (2H, t, J = 5,7 Hz), 3,50 (2H, t, J = 6,3 Hz), 3,23 (2H, q, J = 6,9 Hz), 1,38 (9H, s), 1,12-1,00 (3H, m).

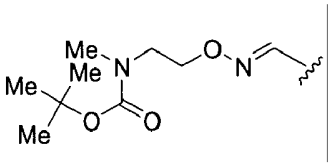
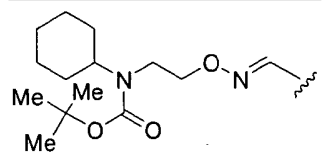
O composto seguinte foi sintetizado de acordo com o mesmo modo que o do primeiro passo acima.

Fórmula química 62

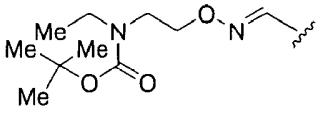
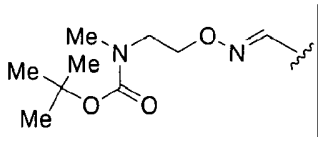
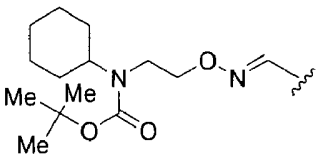


(V)

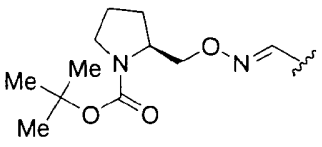
Quadro 3

Nº do Composto	R^A	R^B	RMN de ^1H (d_6-DMSO)
V-18	Cl		9,92(1H, s), 8,62(1H, s), 8,60(1H, s), 8,34(1H, s), 8,12(1H, d, J = 8,4 Hz), 8,00(1H, d, J = 2,4 Hz), 7,79(1H, d, J = 8,7 Hz), 7,72(1H, dd, J = 2,4 Hz, J = 8,7 Hz), 7,47(1H, dt, J = 6,0 Hz, J = 7,8 Hz), 7,36-7,30(2H, m), 7,28(1H, d, J = 9,0 Hz), 7,23-7,14(1H, m), 5,26(2H, s), 4,28(2H, t, J = 5,7 Hz), 3,57-3,48(2H, m), 2,84(3H, s l), 1,36(9H, s).
V-19	Cl		9,92(1H, s), 8,63(1H, s), 8,60(1H, s), 8,33(1H, s), 8,12(1H, dd, J = 1,5 Hz, J = 9,0 Hz), 8,01(1H, d, J = 2,4 Hz), 7,80(1H, d, J = 8,7 Hz), 7,72(1H, dd, J = 2,7 Hz, J = 9,0 Hz), 7,47(1H, dt, J = 6,0 Hz, J = 7,8 Hz), 7,36-7,30(2H, m), 7,28(1H, d, J = 9,0 Hz), 7,22-7,14(1H, m), 5,26(2H, s), 4,21(2H, t, J = 6,0 Hz), 3,8-3,5(1H, s l), 3,48-3,37(2H, m), 1,8-1,4(6H, m), 1,35-1,0(4H, m).

(continuação)

Nº do Composto	R^A	R^B	RMN de ^1H (d_6-DMSO)
V-20	OMe		9,83(1H, s), 8,64(1H, s), 8,57(1H, s), 8,34(1H, s), 8,12(1H, dd, J = 1,5 Hz, J = 8,7 Hz), 7,78(1H, d, J = 8,7 Hz), 7,50-7,36(3H, m), 7,34-7,26(2H, m), 7,21-7,13(1H, m), 7,06(1H, d, J = 8,7 Hz), 5,13(2H, s), 4,26(2H, t, J = 5,7 Hz), 3,82(3H, s), 3,50(2H, t, J = 5,7 Hz), 3,23(2H, q, J = 7,2 Hz), 1,38(9H, s), 1,12-1,02(3H, m).
V-21	OMe		9,84(1H, s), 8,63(1H, s), 8,56(1H, s), 8,36(1H, s), 8,12(1H, dd, J = 1,5 Hz, J = 8,7 Hz). 7,77(1H, d, J = 8,7 Hz), 7,50-7,35(3H, m), 7,33-7,25(2H, m), 7,20-7,12(1H, m), 7,05(1H, d, J = 8,7 Hz), 5,13(2H, s), 4,27(2H, t, J = 5,7 Hz), 3,82(3H, s), 3,55-3,47(2H, m), 2,84(3H, s l), 1,36(9H, s).
V-22	OMe		9,82(1H, s), 8,64(1H, s), 8,56(1H, s), 8,33(1H, s), 8,11(1H, dd, J = 1,5 Hz, J = 8,7 Hz), 7,78(1H, d, J = 8,7 Hz), 7,50-7,36(3H, m), 7,33-7,26(2H, m), 7,21-7,12(1H, m), 7,05(1H, d, J = 8,7 Hz), 5,13(2H, s), 4,21(2H, t, J = 6,6 Hz), 3,82(3H, s), 3,8-3,5(1H, m), 3,47-3,35(2H, m), 1,8-1,35(6H. m), 1,41(9H, s), 1,35-0,95(4H, m).

(continuação)

Nº do Composto	R^A	R^B	RMN de ^1H (d_6-DMSO)
V-28	Cl		9,91(1H, s), 8,62(1H, s l), 8,60(1H, s), 8,36(1H, s), 8,10(1H, dd, J = 8,7 Hz), 8,01(1H, s l), 7,79(1H, d, J = 8,4 Hz), 7,73(1H, d, J = 8,1 Hz), 7,52-7,44(1H, m), 7,35-7,27(3H, m), 7,19(1H, dt, J = 8,1 Hz, J = 2,4 Hz), 5,26(2H, s), 4,28(1H, s l), 4,17(1H, dd, J = 10,5 Hz, J = 6,9 Hz), 4,00(1H, s l), 3,25(3H, l), 1,92 (3H, l), 1,80 (1H, l), 1,43(9H, s)

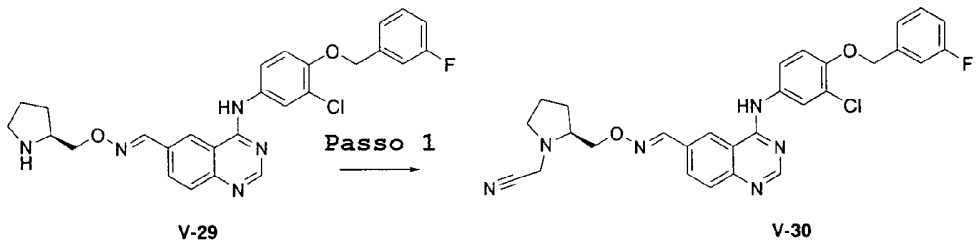
Passo 2 Síntese de 4-(3-cloro-4-(3-fluorobenziloxi)-fenilamino)-6-(2-(N-etilamino)etiloxiimino)quinazolina (V-17)

Em clorofórmio (1,8 mL) foi dissolvido 4-(3-cloro-4-(3-fluorobenziloxi)fenilamino)-6-(2-(N-(t-butoxicarbonil)-N-etilamino)etiloxiimino)quinazolina (V-16, 54 mg) e foi adicionado ácido trifluoroacético (1,8 mL), seguido de agitação à temperatura ambiente durante 1 hora. Depois de a reacção estar completa, a mistura reaccional foi concentrada e diluída com acetato de etilo. A mistura foi sequencialmente lavada com solução aquosa saturada de bicarbonato de sódio, água e solução aquosa de clorito de sódio, e seca sobre sulfato de magnésio. Após concentração, o resíduo cristalino foi lavado com uma mistura de diclorometano-hexano (1:4) para obter 4-(3-cloro-4-(3-fluorobenziloxi)fenilamino)-6-(2-(N-etilamino)etiloxiimino)quinazolina (V-17, 28 mg) como um sólido branco.

RMN de ^{1}H (d_6-DMSO, δ): 9,96 (1H, s), 8,65 (1H, s l), 8,60 (1H, s), 8,35 (1H, s), 8,11 (1H, d, J = 9,0 Hz), 8,01 (1H, d, J = 3,0 Hz), 7,80 (1H, d, J = 9,0 Hz), 7,75-7,70 (1H, m), 7,52-7,43 (1H, m), 7,36-7,31 (2H, m), 7,28 (1H, d, J = 9,3 Hz), 7,23-7,14 (1H, m), 5,26 (2H, s), 4,26 (2H, t, J = 6,0 Hz), 2,93 (2H, t, J = 6,0 Hz), 2,66 (2H, q, J = 7,2 Hz), 1,05 (3H, t, J = 7,2 Hz).

Exemplo 3

Fórmula química 63



V-29 V-30

Passo 1 Síntese de 4-(3-cloro-4-(3-fluorobenziloxi)fenilamino)-6-(1-(N-cianometilpirrolidin-2-il)metoxiimino)metilquinazolina (V-30)

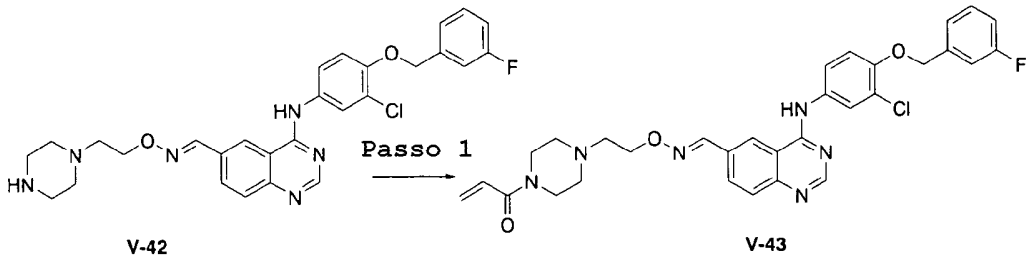
Em 0,4 mL de N,N-dimetilacetamida foram dissolvidos 40 mg de Composto V-29 e 8 µL de iodoacetonitrilo, e foi adicionado 15 mg de carbonato de potássio, seguido de agitação à temperatura ambiente durante 1 hora. Após a reacção, foi adicionada solução aquosa saturada de cloreto de sódio, seguida de extracção com acetato de etilo. A camada orgânica foi desidratada passando através de Presep (marca registada) e o

filtrado foi concentrado. O resíduo concentrado foi purificado por cromatografia sobre sílica gel (eluindo com hexano: acetato de etilo = 2:1) para obter 35 mg de 4-(3-cloro-4-(3-fluorobenziloxi)fenilamino)-6-(1-(N-cianometilpirrolidin-2-il)metoxiimino)metilquinazolina (V-30).

RMN de ^{1}H (d_6-DMSO, δ): 9,92 (1H, s), 8,62 (1H, d, J = 1,5 Hz), 8,58 (1H, s), 8,36 (1H, s), 8,09 (1H, dd, J = 8,7 Hz, J = 1,5 Hz), 7,99 (1H, d, J = 2,6 Hz), 7,78 (1H, d, J = 8,7 Hz), 7,71 (1H, dd, J = 9,0 Hz, J = 2,6 Hz), 7,49-7,42 (1H, m), 7,33-7,25 (3H, m), 7,16 (1H, dt, J = 8,1 Hz, J = 1,8 Hz), 5,24 (2H, s), 4,17 (2H, d, J = 5,7 Hz), 3,97 (1H, d, J = 17 Hz), 3,90 (1H, d, J = 17 Hz), 3,00-2,89 (2H, m), 2,01-1,89 (1H, m), 1,78-1,54 (3H, m).

Exemplo 4

Fórmula química 64



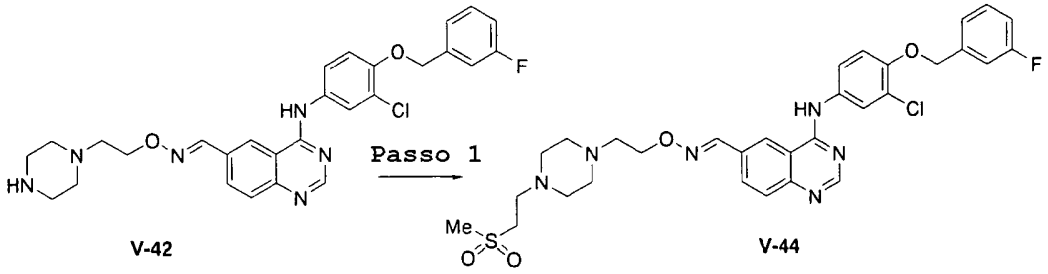
Passo 1 Síntese de 4-(3-cloro-4-(3-fluorobenziloxi)-fenilamino)-6-(2-(4-acriloil-1-piperazin-1-il)etoxiimino)metil-quinazolina (V-43)

Em 1,5 mL de tetra-hidrofurano foram dissolvidos 40 mg de Composto V-42 e 6 µL de cloreto de acriloílo, seguido de agitação à temperatura ambiente durante 2 horas. Após a reacção, foi adicionada solução aquosa saturada de cloreto de sódio, seguida de extracção com acetato de etilo. A camada orgânica foi desidratada passando através de CHEM ELUT (nome comercial) e o filtrado foi concentrado. O resíduo concentrado foi purificado por cromatografia (eluindo com 1% metanol contendo acetato de etilo) e o resíduo resultante foi solidificado com hexano-acetato de etilo (6:1) para obter 20 mg de 4-(3-cloro-4-(3-fluorobenziloxi)fenilamino)-6-(2-(4-acriloil-1-piperazin-1-il)etoxiimino)metilquinazolina (V-43).

RMN de ^{1}H (d_6-DMSO, δ): 9,95 (1H, s), 8,64 (1H, s), 8,59 (1H, s), 8,35 (1H, s), 8,10 (1H, d, J = 8,7 Hz), 8,00 (1H, d, J = 2,4 Hz), 7,78 (1H, d, J = 8,7 Hz), 7,72 (1H, dd, J = 9,0 Hz, 2,7 Hz), 7,44-7,51 (1H, m), 7,26-7,35 (3H, m), 7,15-7,22 (1H, m), 6,79 (1H, dd, J = 16,5 Hz, 10,2 Hz), 6,10 (1H, dd, J = 16,5 Hz, 2,4 Hz), 6,17 (1H, dd, J = 10,5 Hz, 2,4 Hz), 5,26 (2H, s), 4,32 (2H, t, J = 5,7 Hz), 3,55 (4H, m), 2,72 (2H, t, J = 5,7 Hz), 2,50 (4H, m)

Exemplo 5

Fórmula química 65



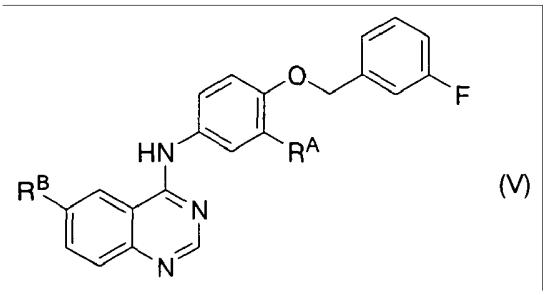
Passo 1 Síntese de 4-(3-cloro-4-(3-fluorobenziloxi)fenilamino)-6-(2-(4-(2-metanossulfoniletil)-1-piperazin-1-il)etoxiimino)metilquinazolina (V-44)

Em 1mL de tetra-hidrofurano foram dissolvidos 25 mg de Composto V-42 e 4 µL de metilvinilsulfona, seguido de agitação à temperatura ambiente durante 21 horas. Além disso, foram adicionados 4 µL de metilvinilsulfona, seguido de agitação à temperatura ambiente durante 29 horas. Após a reacção, foi adicionada solução aquosa saturada de cloreto de sódio, seguida de extracção com acetato de etilo. A camada orgânica foi lavada sequencialmente com água e solução aquosa saturada de cloreto de sódio, e seca sobre sulfato de magnésio. O resíduo concentrado foi purificado por cromatografia (eluindo com acetato de etilo) utilizando uma coluna amino e o resíduo resultante foi solidificado com hexano-acetato de etilo (6:1) para obter 15 mg de 4-(3-cloro-4-(3-fluorobenziloxi)fenilamino)-6-(2-(4-(2-metanossulfoniletil)-1-piperazin-1-il)etoxiimino)metil-quinazolina (V-44).

RMN de ^{1}H (d_6-DMSO, δ): 9,95(1H, s), 8,63(1H, s), 8,59(1H, s), 8,34(1H, s), 8,10(1H, d, J = 9,6 Hz), 8,00 (1H, d, J = 2,4 Hz), 7,79 (1H, d, J = 8,4 Hz), 7,71 (1H, dd, J = 8,7 Hz, 2,7 Hz), 7,44-7,51 (1H, m), 7,26-7,34 (3H, m), 7,15-7,22 (1H, m), 5,26 (2H, s), 4,29 (2H, t, J = 6,0 Hz), 3,27 (2H, t, J = 6,6 Hz), 3,02 (3H, s), 2,67-2,70 (4H, m), 2,46 (8H, m)

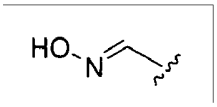
O composto seguinte foi sintetizado de acordo com o mesmos métodos que os dos Exemplos 1 a 5.

Fórmula química 66

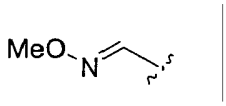
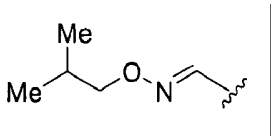


(V)

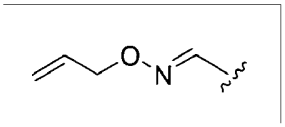
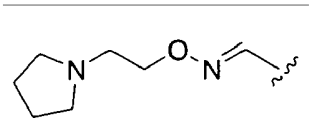
Quadro 4

N° do Composto	R^A	R^B	RMN de ^{1}H (d_6-DMSO)
V-2	Cl		11,69(1H,s), 11,11(1H, s l), 8,84(1H, s), 8,83(1H, s), 8,29(1H, s), 8,26(1H, d, J = 8,7 Hz), 7,95(1H, d, J = 2,7 Hz), 7,88(1H, d, J = 8,7 Hz), 7,67(1H, dd, J = 2,3 Hz, J = 9,2 Hz), 7,48(1H, dt, J = 6,0 Hz, J = 7,8 Hz), 7,37-7,29(3H, m), 7,20(1H, t l, J = 9,2 Hz), 5,30(2H, s).

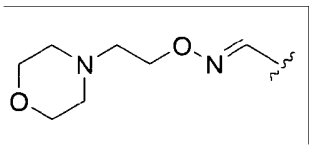
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Nº do Composto	R^A	R^B	RMN de ^1H (d_6-DMSO)
V-3	Cl		9,96(1H, s), 8,65(1H, s), 8,60(1H, s), 8,34(1H, s), 8,10(1H, d l, J = 8,7 Hz), 8,01(1H, d, J = 2,4 Hz), 7,79(1H, d, J = 8,4 Hz), 7,73(1H, dd, J = 2,7 Hz, J = 9,0 Hz), 7,48(1H, dt, J = 6,0 Hz, J = 8,1 Hz), 7,36-7,31(2H, m), 7,28(1H, d, J = 9,0 Hz), 7,19(1H, t l, J = 8,7 Hz), 5,26(2H, s), 3,98(3H, s).
V-4	Cl		9,95(1H, s), 8,63(1H, s), 8,60(1H, s), 8,36(1H, s), 8,10(1H, dd, J = 8,7 Hz, J = 1,2 Hz), 8,01(1H, d, J = 2,4 Hz), 7,79(1H, d, J = 8,4 Hz), 7,72(1H, dd, J = 2,6 Hz, J = 8,9 Hz), 7,48(1H, dt, J = 6,0 Hz, J = 8,1 Hz), 7,36-7,29(2H, m), 7,28(1H, d, J = 9,0 Hz), 7,19(1H, dt, J = 2,4 Hz, J = 8,6 Hz), 5,27(2H, s), 3,97(2H, d, J = 6,9 Hz), 2,05(1H, m), 0,95(6H, d, J = 6,9 Hz).

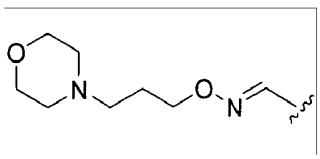
(continuação)

Nº do Composto	R^A	R^B	RMN de ^1H (d_6-DMSO)
V-5	Cl		9,96(1H, s), 8,64(1H, s), 8,60(1H, s), 8,39(1H, s), 8,11(1H, dd, J = 1,5 Hz, J = 8,7 Hz), 8,01(1H, d, J = 2,7 Hz), 7,79(1H, d, J = 8,7 Hz), 7,72(1H, dd, J = 2,7 Hz, J = 9,0 Hz), 7,48(1H, dt, J = 6,3 Hz, J = 7,8 Hz), 7,36-7,29(2H, m), 7,28(1H, d, J = 9,0 Hz), 7,19(1H, dt, J = 2,2 Hz, J = 8,6 Hz), 6,08(1H, ddt, J = 17,4 Hz, J = 10,5 Hz, J = 5,7 Hz), 5,38(1H, ddd, J = 17,4 Hz, J = 3,6 Hz, J = 1,8 Hz), 5,30-5,24(1H, m), 5,26(2H, s), 4,72(2H, dt, J = 5,7 Hz, J = 1,5 Hz).
V-6	Cl		9,95(1H, s), 8,64(1H, s), 8,60(1H, s), 8,35(1H, s), 8,11(1H, d l, J = 8,7 Hz), 8,00(1H, d, J = 2,7 Hz), 7,79(1H, d, J = 8,7 Hz), 7,72(1H, dd, J = 2,7 Hz, J = 9,0 Hz), 7,51-7,44(1H, m), 7,36-7,31(2H, m), 7,28(1H, d, J = 9,3 Hz), 7,19(1H, t l, J = 8,4 Hz), 5,26(2H, s), 4,29(2H, t, J = 6,3 Hz), 2,810(2H, t, J = 4,8 Hz), 2,6-2,5(4H, m), 1,75-1,65(4H, m).

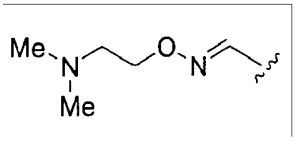
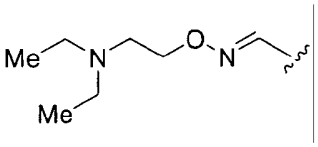
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Nº do Composto	R^A	R^B	RMN de ^1H (d_6-DMSO)
V-7	Cl		9,95(1H, s), 8,64(1H, s), 8,60(1H, s), 8,35(1H, s), 8,11(1H, dd, J = 8,7 Hz, J = 1,5 Hz), 8,01(1H, d, J = 2,7 Hz), 7,80(1H, d, J = 9,0 Hz), 7,72(1H, dd, J = 9,0 Hz, J = 2,7 Hz), 7,48(1H, dt, J = 6,0 Hz, J = 8,1 Hz), 7,36-7,31(2H, m), 7,28(1H, d, J = 9,3 Hz), 7,19(1H, t l J = 9,0 Hz), 5,27(2H, s), 4,31(2H, t, J = 5,7 Hz), 3,58(4H, t, J = 5,1 Hz), 2,67(2H, t, J = 5,7 Hz), 2,46(4H, t, J = 4,5 Hz).

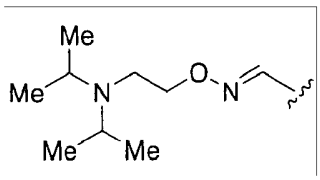
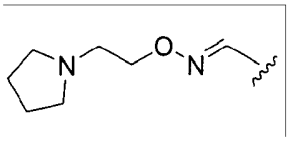
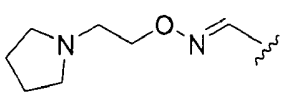
Quadro 5

Nº do Composto	R^A	R^B	RMN de ^1H (d_6-DMSO)
V-8	-Cl		9,94(1H, s), 8,63(1H, s), 8,59(1H, s), 8,33(1H, s), 8,10(1H, d l, J = 7,2 Hz), 8,00(1H, d, J = 2,4 Hz), 7,78(1H, d, J = 8,7 Hz), 7,71(1H, dd, J = 8,7 Hz, J = 2,1 Hz), 7,47(1H, dt, J = 6,3 Hz, J = 8,1 Hz), 7,36-7,31(2H, m), 7,28(1H, d, J = 9,0 Hz), 7,18(1H, t l, J = 9,0 Hz), 5,26(2H, s), 4,23(2H, t, J = 6,3 Hz), 3,57(4H, t, J = 4,5 Hz), 2,45-2,35(6H, m), 1,87(2H, quin, J = 6,8 Hz).

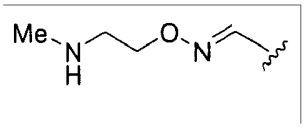
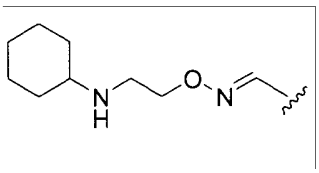
(continuação)

Nº do Composto	R^A	R^B	RMN de ^1H (d_6-DMSO)
V-9	-Cl		9,95(1H, s), 8,63(1H, s), 8,60(1H, s), 8,34(1H, s), 8,11(1H, dd, J = 8,7 Hz, J = 1,5 Hz), 8,00(1H, d, J = 2,7 Hz), 7,79(1H, d, J = 8,7 Hz), 7,72(1H, dd, J = 8,7 Hz, J = 2,7 Hz), 7,48(1H, dt, J = 6,0 Hz, J = 8,1 Hz), 7,36-7,31(2H, m), 7,28(1H, d, J = 9,0 Hz), 7,18(1H, dt, J = 2,4 Hz, J = 8,4 Hz), 5,26(2H, s), 4,28(2H, t, J = 5,7 Hz), 2,63(2H, t, J = 5,7 Hz), 2,23(6H, s).
V-10	-Cl		9,93(1H, s), 8,63(1H, s), 8,60(1H, s), 8,33(1H, s), 8,11(1H, dd, J = 8,7 Hz, J = 1,5 Hz), 8,01(1H, d, J = 2,4 Hz), 7,79(1H, d, J = 8,7 Hz), 7,72(1H, dd, J = 2,7 Hz, J = 8,7 Hz), 7,47(1H, dt, J = 5,7 Hz, J = 8,1 Hz), 7,36-7,31(2H, m), 7,28(1H, d, J = 9,3 Hz), 7,18(1H, dt, J = 8,7 Hz, J = 2,7 Hz), 5,26(2H, s), 4,25(2H, t, J = 6,2 Hz), 2,79(2H, s l), 2,57(4H, q, J = 6,6 Hz), 0,99(6H, t, J = 7,1 Hz).

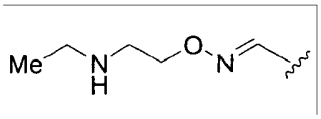
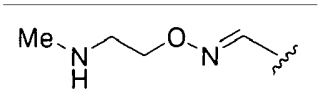
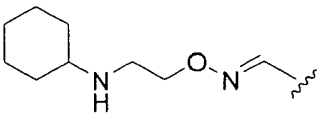
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Nº do Composto	R^A	R^B	RMN de ^1H (d_6-DMSO)
V-11	-Cl		9,91(1H, s), 8,61(1H, d, J = 1,5 Hz), 8,60(1H, s), 8,31(1H, s), 8,12(1H, dd, J = 1,5 Hz, J = 8,7 Hz), 8,01(1H, d, J = 2,4 Hz), 7,79(1H, d, J = 8,7 Hz), 7,72(1H, dd, J = 2,4 Hz, J = 8,7 Hz), 7,47(1H, dt, J = 5,7 Hz, J = 8,1 Hz), 7,36-7,31(2H, m), 7,28(1H, d, J = 9,3 Hz), 7,18(1H, dt, J = 8,7 Hz, J = 2,7 Hz), 5,26(2H, s), 4,10(2H, t, J = 6,9 Hz), 3,01(2H, quin, J = 6,3 Hz), 2,74(2H, t, J = 6,9 Hz), 1,99(12H, d, 6,3 Hz).
V-12	-F		9,94(1H, s), 8,64(1H, s), 8,60(1H, s), 8,34(1H, s), 8,11(1H, d, J = 8,8 Hz), 7,88(1H, d, J = 13,2 Hz), 7,79(1H, d, J = 8,8 Hz), 7,56-7,44(2H, m), 7,36-7,24(3H, m), 7,19(1H, t l, J = 8,8 Hz), 5,18(2H, s), 4,32-4,27(2H, m), 2,82-2,74(2H, m), 2,55-2,48(4H, m), 1,73-1,65(4H, m).
V-13	-OMe		9,84(1H, s), 8,64(1H, d, J = 1,5 Hz), 8,55(1H, s), 8,34(1H, s), 8,09(1H, dd, J = 1,5 Hz, J = 8,7 Hz), 7. 77(1H, d, J = 8,7 Hz), 7,49-7,36(3H, m), 7,33-7,26(2H, m), 7,20-7,12(1H, m), 7,05(1H, d, J = 9,0 Hz), 5,13(2H, s), 4,28(2H, t, J = 6,0 Hz), 3,82(3H, s), 2,76(2H, t, J = 6,0 Hz), 2,54-2,46(4H, m), 1,76-1,62(4H, m).

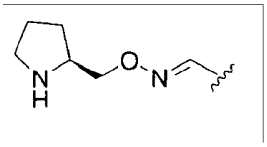
Quadro 6

Nº do Composto	R^A	R^B	RMN de ^1H (d_6-DMSO)
V-23	Cl		9,96(1H, s), 8,64(1H, s), 8,60(1H, s), 8,34(1H, s), 8,11(1H, dd, J = 1,2 Hz, J = 8,4 Hz), 8,01(1H, d, J = 2,4 Hz), 7,79(1H, d, J = 8,7 Hz), 7,72(1H, dd, J = 2,4 Hz, J = 8,7 Hz), 7,48(1H, dt, J = 6,0 Hz, J = 8,4 Hz), 7,36-7,30(2H, m), 7,28(1H, d, J = 9,0 Hz), 7,23-7,15(1H, m), 5,27(2H, s), 4,24(2H, t, J = 5,7 Hz), 2,81(2H, t, J = 5,7 Hz), 2,33(3H, s).
V-24	Cl		9,95(1H, s), 8,65(1H, d, J = 1,2 Hz), 8,60(1H, s), 8,35(1H, s), 8,11(1H, dd, J = 1,5 Hz, J = 8,7 Hz), 8,01(1H, d, J = 2,7 Hz), 7,79(1H, d, J = 8,7 Hz), 7,73(1H, dd, J = 2,7 Hz, J = 9,0 Hz), 7,47(1H, dt, J = 6,0 Hz, J = 8,1 Hz), 7,36-7,30(2H, m), 7,28(1H, d, J = 9,0 Hz), 7,23-7,14(1H, m), 5,26(2H, s), 4,25(2H, t, J = 5,7 Hz), 2,95(2H, t, J = 5,7 Hz), 2,55-2,4(1H, m), 1,9-1,8(2H, m), 1,75-1,62(2H, m), 1,6-1,5(1H, m), 1,3-0,97(5H, m).

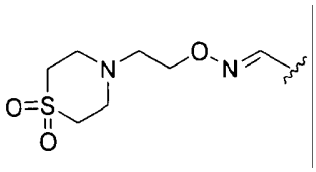
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Nº do Composto	R^A	R^B	RMN de ^1H (d_6-DMSO)
V-25	OMe		9,86(1H, s), 8,64(1H, s), 8,56(1H, s), 8,34(1H, s), 8,10(1H, d, J = 8,4 Hz), 7,77(1H, d, J = 8,7 Hz), 7,5-7,35(3H, m), 7,34-7,26(2H, m), 7,21-7,13(1H, m), 7,06(1H, d, J = 8,7 Hz), 5,13(2H, s), 4,23(2H, t, J = 6,0 Hz), 3,82(3H, s), 2,86(2H, t, J = 6,0 Hz), 2,59(2H, q, J = 7,2 Hz), 1,02(3H, t, J = 7,2 Hz).
V-26	OMe		9,86(1H, s), 8,64(1H, s), 8,56(1H, s), 8,33(1H, s), 8,10(1H, d, J = 8,7 Hz), 7,77(1H, d, J = 9,0 Hz), 7,50-7,35(3H, m), 7,33-7,26(2H, m), 7,21-7,13(1H, m), 7,05(1H, d, J = 8,4 Hz), 5,13(2H, s), 4,23(2H, t, J = 5,7 Hz), 3,82(3H, s), 2,81(2H, d, J = 6,0 Hz), 2,33(3H, s).
V-27	Ome		9,86(1H, s), 8,64(1H, s), 8,56(1H, s), 8,34(1H, s), 8,09(1H, dd, J = 1,5 Hz, J = 8,7 Hz), 7,77(1H, d, J = 8,7 Hz), 7,50-7,35(3H, m), 7,33-7,26(2H, m), 7,21-7,13(1H, m), 7,05(1H, d, J = 8,7 Hz), 5,13(2H, s), 4,22(2H, t, J = 5,7 Hz), 3,82(3H, s), 2,88(2H, t, J = 5,7 Hz), 2,45-2,35(1H, m), 1,88-1,76(2H, m), 1,72-1,62(2H, m), 1,6-1,5(2H, m), 1,3-0,93(4H, m).

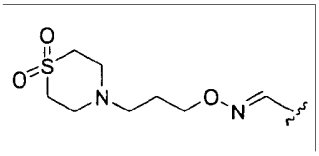
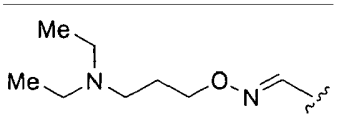
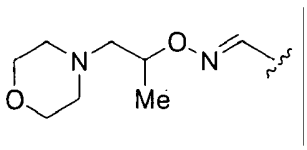
(continuação)

Nº do Composto	R^A	R^B	RMN de ^1H (d_6-DMSO)
V-29	Cl		9,94(1H, s), 8,65(1H, s l), 8,60(1H, s), 8,35(1H, s), 8,11(1H, dd, J = 8,7 Hz, J = 1,2 Hz), 8,00(1H, d, J = 2,4 Hz), 7,79(1H, d, J = 8,7 Hz), 7,72(1H, dd, J = 9,0 Hz, J = 2,1 Hz), 7,51-7,44(1H, m), 7,35-7,27(3H, m), 7,18(1H, dt, J = 8,1 Hz, J = 1,5 Hz), 5,26(2H, s), 4,12(2H. d, J = 6,3 Hz), 3,53-3,44(1H, m), 2,96-2,82(2H, m), 1,94-1,64(3H, m), 1,53-1,41(1H, m)

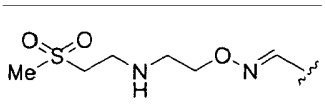
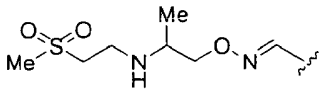
Quadro 7

Nº do Composto	R^A	R^B	RMN de ^1H (d_6-DMSO)
V-30	-Cl		9,95(1H, s), 8,64(1H, s), 8,59(1H, s), 8,35(1H, s), 8,11(1H, d, J = 8,7 Hz), 8,00(1H, d, J = 2,4 Hz), 7,79(1H, d, J = 8,7 Hz), 7,71(1H, dd, J = 8,4 Hz, J = 1,8 Hz), 7,44-7,51(1H, m), 7,26-7,35(3H, m), 7,15-7,22(1H, m), 5,26(2H, s), 4,31(2H, t, J = 5,7 Hz), 3,08-3,10(4H, m), 3,02-3,04(4H, m), 2,91(2H, t, J = 5,7 Hz)

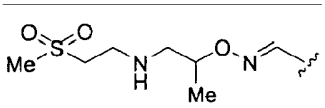
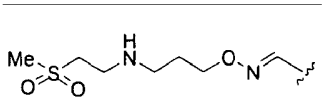
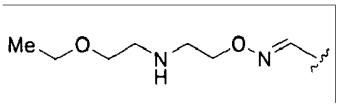
(continuação)

Nº do Composto	R^A	R^B	RMN de ^1H (d_6-DMSO)
V-31	-Cl		9,95(1H, s), 8,63(1H, s), 8,60(1H, s), 8,34(1H, s), 8,11(1H, d, J = 9,3 Hz), 8,00(1H, d, J = 2,7 Hz), 7,79(1H, d, J = 8,7 Hz), 7,72(1H, dd, J = 9,0 Hz, J = 2,4 Hz), 7,51-7,44(1H, m), 7,35-7,27(3H, m), 7,22-7,15(1H, m), 5,26(2H, s), 4,23(2H, t, J = 6,3 Hz), 3,09-3,07(4H, m), 2,92-2,90(4H, m), 2,59(2H, t, J = 6,9 Hz), 1,90-1,85(2H, m)
V-32	-Cl		9,94(1H, s), 8,64(1H, s), 8,59(1H, s), 8,33(1H, s), 8,10(1H, d, J = 8,7 Hz), 8,00(1H, d, J = 2,7 Hz), 7,79(1H, d, J = 8,7 Hz), 7,72(1H, dd, J = 8,7 Hz, 2,4 Hz), 7,44-7,51(1H, m), 7,26-7,35(3H, m), 7,15-7,22(1H, m), 5,26(2H, s), 4,22(2H, t, J = 6,3 Hz), 2,49-2,51(6H, m), 1,78-1,83(2H, m), 0,95(6H, t, J = 7,2 Hz)
V-33	-Cl		9,94(1H, s), 8,61(1H, s), 8,59(1H, s), 8,31(1H, s), 8,11(1H, dd, J = 8,4 Hz,1,5 Hz), 8,00(1H, d, J = 2,7 Hz), 7,79(1H, d, J = 8,7 Hz), 7,71(1H, dd, J = 9,3 Hz, 2,7 Hz), 7,44-7,51(1H, m), 7,26-7,35(3H, m), 7,15-7,22(1H, m), 5,26(2H, s), 4,50-4,56(1H, m), 3,57(4H, t, J = 4,8 Hz), 2,59-2,65(2H, m), 2,46(4H, m), 1,31(3H, d, J = 6,0 Hz)

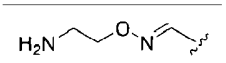
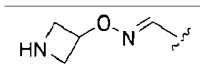
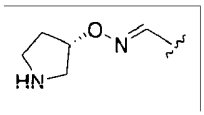
(continuação)

Nº do Composto	R^A	R^B	RMN de ^1H (d_6-DMSO)
V-34	-Cl		9,95(1H, s), 8,65(1H, s), 8,60(1H, s), 8,34(1H, s), 8,12(1H, dd, J = 9,0 Hz, 1,8 Hz), 8,01(1H, d, J = 2,7 Hz), 7,79(1H, d, J = 8,7 Hz), 7,72(1H, dd, J = 8,7 Hz, J = 2,4 Hz), 7,44-7,52(1H, m), 7,27-7,35(3H, m), 7,16-7,22(1H, m), 5,27(2H, s), 4,25(2H, t, J = 5,4 Hz), 3,25(2H, t, J = 6,9 Hz), 3,02(3H, s), 2,99(2H, t, J = 6,9 Hz), 2,89(2H, t, J = 5,7 Hz)
V-35	-Cl		9,95(1H, s), 8,65(1H, s), 8,60(1H, s), 8,36(1H, s), 8,12(1H, dd, J = 8,7 Hz, 1,8 Hz), 8,01(1H, d, J = 2,7 Hz), 7,80(1H, d, J = 8,7 Hz), 7,72(1H, dd, J = 9,0 Hz, 2,4 Hz), 7,44-7,52 (1H, m), 7,27-7,35(3H, m), 7,16-7,22(1H, m), 5,27(2H, s), 4,04-4,09(2H, m), 3,20-3,26(2H, m), 2,98-3,08(6H, m), 1,06(3H, d, J = 6,3 Hz)

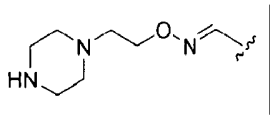
Quadro 8

Nº do Composto	R^A	R^B	RMN de ^1H (d_6-DMSO)
V-36	-Cl		9,95(1H, s), 8,63(1H, s), 8,60(1H, s), 8,32(1H, s), 8,13(1H, d, J = 9,0 Hz), 8,00(1H, d, J = 2,7 Hz), 7,80(1H, d, J = 8,4 Hz), 7,72(1H, dd, J = 9,3 Hz, 2,7 Hz), 7,44-7,52(1H, m), 7,27-7,35(3H, m), 7,16-7,22(1H, m), 5,27(2H, s), 4,40-4,46(1H, m), 3,27(2H, t, J = 6,9 Hz), 2,99-3,02(5H, m), 2,74-2,90(2H, m), 1,30(3H, d, J = 6,6 Hz)
V-37	-Cl		9,95(1H, s), 8,64(1H, s), 8,60(1H, s), 8,34(1H, s), 8,11(1H, dd, J = 9,0 Hz, 1,2 Hz), 8,01(1H, d, J = 2,7 Hz), 7,79(1H, d, J = 8,7 Hz), 7,72(1H, dd, J = 8,7 Hz, 2,7 Hz), 7,44-7,51(1H, m), 7,26-7,34 (3H, m), 7,16-7,22(1H, m), 5,26(2H, s), 4,25 (2H, t, J = 6,3 Hz), 3,25(2H, t, J = 7,2 Hz), 3,03 (3H, s), 2,98(2H, t, J = 6,9 Hz), 2,70(2H, t, J = 6,9 Hz), 1,84-1,91(2H, m)
V-38	-Cl		9,96(1H, s), 8,64(1H, s), 8,60(1H, s), 8,35(1H, s), 8,11(1H, dd, J = 8,7 Hz, 1,5 Hz), 8,01(1H, d, J = 2,4 Hz), 7,79(1H, d, J = 8,7 Hz), 7,73(1H, dd, J = 9,0 Hz, 2,7 Hz), 7,44-7,52(1H, m), 7,27-7,35 (3H, m), 7,16-7,22(1H, m), 5,27(2H, s), 4,25 (2H, t, J = 5,4 Hz), 3,38-3,46(4H, m), 2,91(2H, t, J = 5,7 Hz), 2,73(2H, t, J = 5,4 Hz), 1,09(3H, t, J = 6,9 Hz)

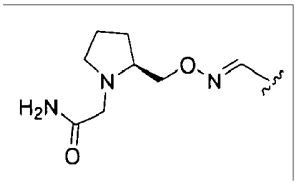
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Nº do Composto	R^A	R^B	RMN de ^1H (d_6-DMSO)
V-39	-Cl		9,96(1H, s), 8,63(1H, s l), 8,60(1H, s), 8,34(1H, s), 8,11(1H, dd, J = 8,7 Hz, J = 1,5 Hz), 8,00(1H, d, J = 2,4 Hz), 7,79(1H, d, J = 8,7 Hz), 7,72(1H, dd, J = 9,0 Hz, J = 2,4 Hz), 7,52-7,44 (1H, m), 7,35-7,27(3H, m), 7,20(1H, dt, J = 9,3 Hz, J = 2,7 Hz), 5,27(2H, s), 4,37(2H, t, J = 6,0 Hz), 3,51(2H, t, J = 6,0 Hz)
V-40	-Cl		9,95(1H, s), 8,64(1H, s l), 8,59(1H, s), 8,40 (1H, s), 8,09(1H, d, J = 6,6 Hz), 8,01(1H, s l), 7,78(1H, d, J = 6,3 Hz), 7,72(1H, d, J = 6,3 Hz), 7,50-7,45(1H, m), 7,35-7,26(3H, m), 7,19(1H, t, J = 6,3 Hz), 5,26(2H, s), 5,09(1H, m), 3,69(2H, tipo t, J = 5,1 Hz), 3,60(2H, tipo t, J = 5,1 Hz)
V-41	-Cl		9,93(1H, s), 8,62(1H, s l), 8,59(1H, s), 8,30 (1H, s), 8,11(1H, d, J = 6,3 Hz), 8,00(1H, d, J = 1,5 Hz), 7,79(1H, d, J = 6,6 Hz), 7,72(1H, dd, J = 6,6 Hz, J = 1,8 Hz), 7,50-7,45(1H, m), 7,35-7,27(3H, m), 7,19(1H, t, J = 5,7 Hz), 5,26(2H, s), 4,88(1H, s l), 3,01-2,88(3H, m), 2,79-2,73(1H, m), 1,99-1,85(2H, m)

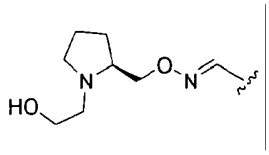
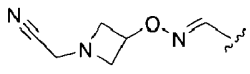
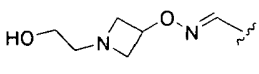
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Nº do Composto	R^A	R^B	RMN de ^1H (d_6-DMSO)
V-42	-Cl		9,95(1H, s), 8,63(1H, s l), 8,60(1H, s), 8,35 (1H, s), 8,11(1H, dd, J = 8,7 Hz, J = 1,5 Hz), 8,01(1H, d, J = 2,4 Hz), 7,79(1H, d, J = 8,7 Hz), 7,72(1H, dd, J = 9,3 Hz, J = 2,7 Hz), 7,52-7,44 (1H, m), 7,35-7,27(3H, m), 7,19(1H, dt, J = 9,3 Hz, J = 2,7 Hz), 5,27(2H, s), 4,29(2H, t, J = 6,0 Hz), 2,69(4H, t, J = 4,8 Hz), 2,63(2H, t, J = 6,0 Hz), 2,39(4H, s l)

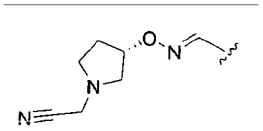
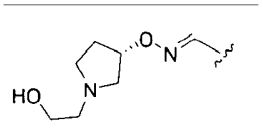
Quadro 9

Nº do Composto	R^A	R^B	RMN de ^1H (d_6-DMSO)
V-45	-Cl		9,93(1H, s), 8,63(1H, s l), 8,60(1H, s), 8,33(1H, s), 8,10(1H, d, J = 6,6 Hz), 8,02(1H, d, J = 1,5 Hz), 7,79(1H, d, J = 6,6 Hz), 7,73(1H, d, J = 6,9 Hz), 7,50-7,45(1H, m), 7,35-7,27(3H, m), 7,19(2H, m), 7,08(1H, s l), 5,26(2H, s), 4,20(1H, dd, J = 8,1 Hz, J = 4,2 Hz), 4,13(1H, dd, J = 8,1 Hz, J = 4,2 Hz), 3,38(1H, d, J = 12 Hz), 3,08-2,93(3H, m), 2,38(1H, m), 199-1,89(1H, m), 1,76-1,57(3H, m)

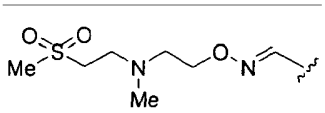
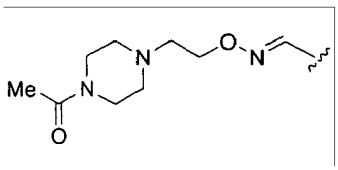
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Nº do Composto	R^A	R^B	RMN de ^1H (d_6-DMSO)
V-46	-Cl		9,93(1H, s), 8,63(1H, s l), 8,60(1H, s), 8,34(1H, s), 8,11(1H, d, J = 6,6 Hz), 8,01(1H, d, J = 2,1 Hz), 7,80(1H, d, J = 6,6 Hz), 7,73(1H, d, J = 8,1 Hz), 7,51-7,44(1H, m), 7,35-7,27(3H, m), 7,19(1H, m), 5,27(2H, s), 4,38(1H, s l), 4,19(1H, dd, J = 8,1 Hz, J = 4,2 Hz), 4,03(1H, dd, J = 8,1 Hz, J = 4,2 Hz), 3,49(2H, dd, J = 9,3 Hz, J = 4,5 Hz), 3,09-3,05(1H, m), 2,95-2,90(1H, m), 2,84-2,82(1H, m), 2,47-2,40(1H, m), 2,29-2,22(1H, m), 1,91-1,85(1H, m), 1,73-1,57(3H, m)
V-47	-Cl		9,94(1H, s), 8,66(1H, s l), 8,60(1H, s), 8,43(1H, s), 8,12(1H, d, J = 6,6 Hz), 8,01(1H, d, J = 1,2 Hz), 7,79(1H, d, J = 6,9 Hz), 7,72(1H, d, J = 6,6 Hz), 7,50-7,45(1H, m), 7,35-7,27(3H, m), 7,19(1H, t, J = 6,0 Hz), 5,27(2H, s), 4,97(1H, m), 3,74(2H, s), 3,68(2H, tipo t, J = 5,1 Hz), 3,37(2H, tipo t, J = 5,1 Hz)
V-48	-Cl		9,95(1H, s), 8,64(1H, s l), 8,60(1H, s), 8,39(1H, s), 8,09(1H, d, J = 6,6 Hz), 8,01(1H, s l), 7,79(1H, d, J = 6,3 Hz), 7,73(1H, d, J = 6,6 Hz), 7,50- 7,45(1H, m), 7,35- 7,27(3H, m), 7,19(1H, t, J = 6,6 Hz), 5,26(2H, s), 4,92(1H, m), 4,42(1H, s l), 3,62(2H, t, J = 5,4 Hz), 3,14(2H, t, J = 5,4 Hz), 2,54(2H, t, J = 4,5 Hz)

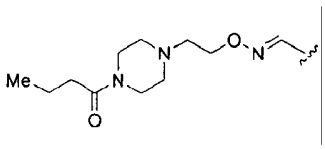
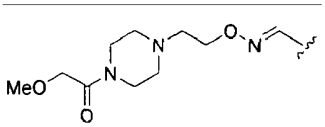
(continuação)

Nº do Composto	R^A	R^B	RMN de ^1H (d_6-DMSO)
V-49	-Cl		9,94(1H, s), 8,63(1H, s l), 8,60(1H, s), 8,32(1H, s), 8,11(1H, d, J = 6,6 Hz), 8,01(1H, d, J = 1,8 Hz), 7,79(1H, d, J = 6,6 Hz), 7,72(1H, dd, J = 6,9 Hz, J = 1,8 Hz), 7,50-7,45(1H, m), 7,35-7,27(3H, m), 7,19(1H, t, J = 6,3 Hz), 5,26(2H, s), 4,95(1H, s l), 3,87(2H, s), 2,91-2,81(3H, m), 2,57-2,51(1H, m), 2,30-2,21(1H, m), 2,00-1,91(1H, m)
V-50	-Cl		9,95(1H, s), 8,62(1H, s l), 8,59(1H, s), 8,32(1H, s), 8,10(1H, d, J = 6,3 Hz), 8,00(1H, s l), 7,79(1H, d, J = 6,3 Hz), 7,72(1H, d, J = 6,3 Hz), 7,50-7,45(1H, m), 7,35-7,27(3H, m), 7,19(1H, t, J = 6,0 Hz), 5,26(2H, s), 4,89(1H, s l), 4,45(1H, s l), 3,49(3H, m), 2,82-2,75(3H, m), 2,41-2,39(1H, m), 2,17(1H, m), 1,86(1H, s l)

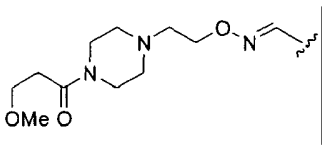
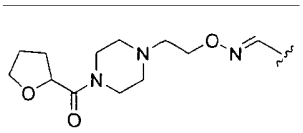
Quadro 10

Nº do Composto	R^A	R^B	RMN de ^1H (d_6-DMSO)
V-51	-Cl		9,94(1H, s), 8,64(1H, s), 8,60(1H, s), 8,33(1H, s), 8,12(1H, d, J = 10,2 Hz), 8,01(1H, d, J = 2,4 Hz), 7,79(1H, d, J = 8,7 Hz), 7,72(1H, dd, J = 8,7 Hz, 2,4 Hz), 7,44-7,51(1H, m), 7,26-7,34(3H, m), 7,16-7,22(1H, m), 5,26(2H, s), 4,29(2H, t, J = 5,7 Hz), 3,27(2H, t, J = 7,2 Hz), 3,02(3H, s), 2,84(2H, t, J = 6,9 Hz), 2,75(2H, t, J = 5,7 Hz), 2,29(3H, s)
V-52	-Cl		9,94(1H, s), 8,64(1H, s), 8,59(1H, s), 8,35(1H, s), 8,10(1H, dd, J = 8,7 Hz, 1,5 Hz), 8,00(1H, d, J = 2,7 Hz), 7,78(1H, d, J = 8,7 Hz), 7,71(1H, dd, J = 8,7 Hz, 2,4 Hz), 7,44-7,51(1H, m), 7,26-7,35(3H, m), 7,15-7,21(1H, m), 5,26(2H, s), 4,32(2H, t, J = 5,7 Hz), 3,42-3,43(4H, m), 2,71(2H, t, J = 5,7 Hz), 2,41(4H, t, J = 5,1 Hz), 1,98(3H, s)

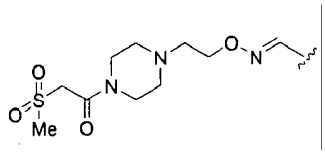
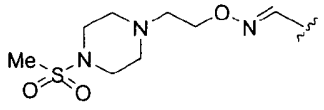
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Nº do Composto	R^A	R^B	RMN de ^1H (d_6-DMSO)
V-53	-Cl		9,95(1H, s), 8,63(1H, s), 8,59(1H, s), 8,35(1H, s), 8,10(1H, dd, J = 8,4 Hz, 1,2 Hz), 8,00(d, 1H, J = 2,4 Hz), 7,79(1H, d, J = 8,4 Hz), 7,71(1H, dd, J = 9,3 Hz, 2,4 Hz), 7,44-7,51(1H, m), 7,26-7,34(3H, m), 7,15-7,22(1H, m), 5,26(2H, s), 4,32(2H, t, J = 5,4 Hz), 3,43-3,45(4H, m), 2,70(2H, t, J = 5,7 Hz), 2,41-2,46(4H, m), 2,26(2H, t, J = 7,2 Hz), 1,43-1,56(2H, m), 0,87(3H, t, J = 7,5 Hz)
V-54	-Cl		9,94(1H, s), 8,63(1H, s), 8,59(1H, s), 8,35(1H, s), 8,10(1H, dd, J = 8,7 Hz, 1,5 Hz), 8,00(1H, d, J = 2,4 Hz), 7,78(1H, d, J = 8,7 Hz), 7,71(1H, dd, J = 9,0 Hz, 2,4 Hz), 7,44-7,51(1H, m), 7,26-7,35(3H, m), 7,15-7,21(1H, m), 5,26(2H, s), 4,32(2H, t, J = 5,7 Hz), 4,06(3H, s), 3,3 7-3,42(4H, m), 3,27(2H, s), 2,71(2H, t, J = 5,7 Hz), 2,46(4H, m)

(continuação)

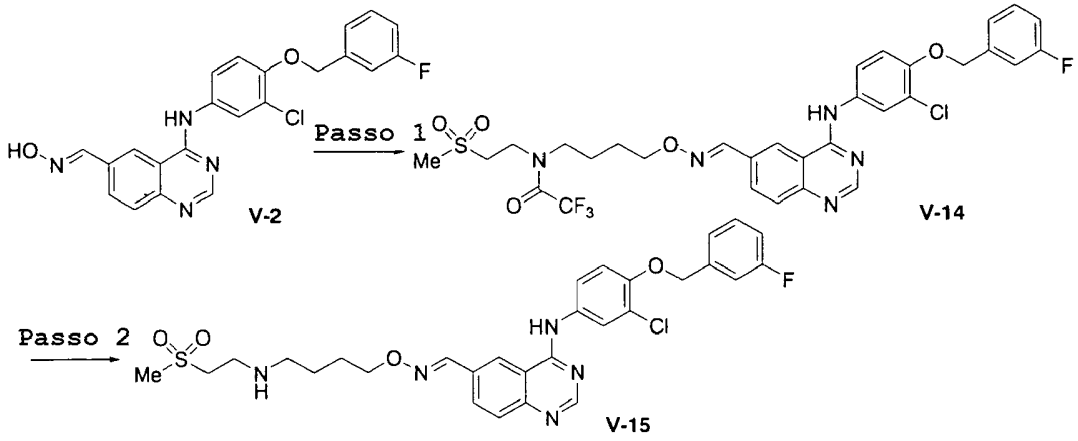
Nº do Composto	R^A	R^B	RMN de ^1H (d_6-DMSO)
V-55	-Cl		9,94(1H, s), 8,63(1H, s), 8,59(1H, s), 8,35(1H, s), 8,10(1H, dd, J = 8,7 Hz, 1,5 Hz), 8,00(1H, d, J = 2,4 Hz), 7,79(1H, d, J = 8,7 Hz), 7,71(1H, dd, J = 9,0 Hz, 2,4 Hz), 7,44-7,51(1H, m), 7,26-7,35(3H, m), 7,15-7,21(1H, m), 5,26(2H, s), 4,32(2H, t, J = 5,7 Hz), 3,53(2H, t, J = 6,6 Hz), 3,43-3,4 7(4H, m), 3,21(3H, s), 2,71(2H, t, J = 6,0 Hz), 2,55(2H, t, J = 6,6 Hz), 2,42-2,50(4H, m)
V-56	-Cl		9,94(1H, s), 8,64(1H, s), 8,59(1H, s), 8,35(1H, s), 8,10(1H, dd, J = 8,7 Hz, 1,5 Hz), 8,00(1H, d, J = 2,7 Hz), 7,79(1H, d, J = 9,0 Hz), 7,71(1H, dd, J = 8,7 Hz, 2,4 Hz), 7,44-7,51(1H, m), 7,26-7,35(3H, m), 7,15-7,22(1H, m), 5,26(2H, s), 4,61-4,66(1H, m), 4,32(2H, t, J = 5,7 Hz), 3,68-3,80(2H, m), 3,44-3,54(4H, m), 2,71(2H, 5,7 Hz), 2,44-2,50(4H, m), 1,95-2,04(2H, m), 1,75-1,86(2H, m)

Quadro 11

Nº do Composto	R^A	R^B	RMN de ^1H (d_6-DMSO)
V-57	-Cl		9,94(1H, s), 8,64(1H, s), 8,59(1H, s), 8,35(1H, s), 8,10(1H, dd, J = 8,7 Hz, 1,2 Hz), 8,00(1H, d, J = 2,7 Hz), 7,79(1H, d, J = 8,7 Hz), 7,71(1H, dd, J = 9,0 Hz, 2,4 Hz), 7,44-7,51(1H, m), 7,26-7,35(3H, m), 7,16-7,21(1H, m), 5,26(2H, s), 4,45(2H, s), 4,32(2H, t, J = 5,4 Hz), 3,49-3,53(4H, m), 3,09(3H, s), 2,72(2H, t, J = 5,7 Hz), 2,44-2,50(4H, m)
V-58	-Cl		9,95(1H, s), 8,64(1H, s), 8,59(1H, s), 8,35(1H, s), 8,10(1H, d, J = 8,7 Hz), 8,00(1H, d, J = 2,7 Hz), 7,78(1H, d, J = 8,7 Hz), 7,69-7,73(1H, m), 7,44-7,51(1H, m), 7,26-7,34(3H, m), 7,16-7,22(1H, m), 5,26(2H, s), 4,31(2H, t, J = 5,7 Hz), 3,12(4H, t, J = 5,1 Hz), 2,87(3H, s), 2,75(2H, t, J = 5,4 Hz), 2,58(4H, t, J = 5,3 Hz)

Exemplo 6

Fórmula química 67



Passo 1 Síntese de 4-(3-cloro-4-(3-fluorobenziloxi)fenilamino)-6-(4-(N-(2-(metanossulfonil)etil)-N-(2,2,2-trifluoroacetil)amino)butiloxiimino)quinazolina (V-14)

Em N,N-dimetilacetamida (1,5 mL) foram dissolvidos 4-(3-cloro-4-(3-fluorobenziloxi)fenilamino)-6-(hidroxiimino)quinazolina (V-2, 84 mg) e N-(4-bromobutil)-N-(2-metanossulfoniletil)-2,2,2-trifluoroacetamida (71 mg), e foi adicionado carbonato de potássio (41 mg), seguido de agitação a 60 °C durante 13 horas com aquecimento. Depois disso, a mistura reaccional foi vertida para ácido cítrico 0,5 M, seguida de extracção com acetato de etilo. A camada orgânica foi lavada com água e solução aquosa de cloreto de sódio, e seca sobre sulfato de magnésio. O produto em bruto foi purificado por cromatografia sobre sílica gel (eluindo com hexano: acetato de etilo = 1:4) para obter 4-(3-cloro-4-(3-fluorobenziloxi)fenilamino)-6-(4-(N-(2-(metanossulfonil)etil)-2,2,2-trifluoroacetamido)butiloxi-imino)quinazolina (V-14, 41 mg) como um sólido amarelo pálido.

RMN de ^{1}H (d_6-DMSO, δ): 9,94 (1H, s), 8,63 (1H, s), 8,59 (1H, s), 8,33 (1H, s), 8,10 (1H, dd, J = 8,4 Hz, J = 1,5 Hz), 8,00 (1H, d, J = 2,4 Hz), 7,78 (1H, d, J = 8,7 Hz), 7,71 (1H, dd, J = 2,3 Hz, J = 8,7 Hz), 7,47 (1H, dt, J = 6,0 Hz, J = 8,1 Hz), 7,36-7,31 (2H, m), 7,28 (1H, d, J = 9,0 Hz), 7,18 (1H, dt, J = 2,0 Hz, J = 8,6 Hz), 5,26 (2H, s), 4,26-4,18 (2H, m), 3,79 (2H, t, J = 7,1 Hz), 3,60-3,44 (4H, m), 3,05 (3H, s), 1,78-1,66 (4H, m).

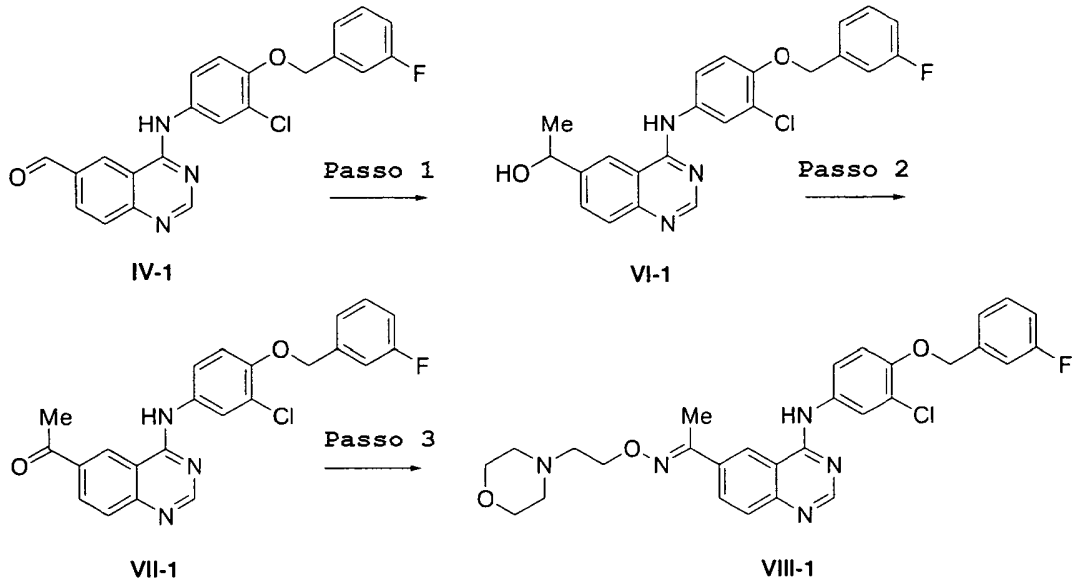
Passo 2 Síntese de 4-(3-cloro-4-(3-fluorobenziloxi)fenilamino)-6-(4-(2-(metanossulfonil)etilamino)butiloxiimino)quinazolina (V-15)

Em 2,6 mL de uma mistura (1:1) de tetra-hidrofurano e metanol foi dissolvido 4-(3-cloro-4-(3-fluorobenziloxi)fenilamino)-6-(4-(N-(2-(metanossulfonil)etil)-2,2,2-trifluoroacetamido)butiloxiimino)quinazolina (V-14, 40 mg) e foram adicionados 86 µL de solução aquosa de hidróxido de sódio a 1 mol/L, seguido de agitação à temperatura ambiente durante 14 horas, e a 40 °C durante 2 hora. Após a reacção, a mistura reaccional foi extraída com acetato de etilo, a camada orgânica foi seca e o filtrado foi concentrado. O resíduo concentrado foi purificado por cromatografia (eluindo com acetato de etilo contendo 0 a 3% de metanol) utilizando uma coluna amino, e o óleo amarelo pálido resultante foi pulverizado com uma mistura de hexano e acetato de etilo para obter 4-(3-cloro-4-(3-iluorobenziloxi)fenilamino)-6-(4-(2-(metanossulfonil)etilamino)butiloxiimino)quinazolina (V-15, 12 mg) como um sólido amarelo pálido.

RMN de ^1H (d_6-DMSO, δ): 9,95 (1H, s), 8,63 (1H, s), 8,59 (1H, s), 8,33 (1H, s), 8,11 (1H, d, J = 8,7 Hz), 8,01 (1H, d, J = 2,4 Hz), 7,79 (1H, d, J = 8,7 Hz), 7,72 (1H, d l, J = 9,0 Hz), 7,51-7,44 (1H, m), 7,36-7,31 (2H, m), 7,28 (1H, d, J = 9,0 Hz), 7,19 (1H, t l, J = 9 Hz), 5,26 (2H, s), 4,20 (2H, t, J = 6,6 Hz), 3,21 (2H, t, J = 6,9 Hz), 2,91 (2H, t, J = 6,6 Hz), 2,56 (2H, t, J = 6,9 Hz), 1,73 (2H, quin, J = 7 Hz), 1,51 (2H, quin, J = 7 Hz).

Exemplo 7

Fórmula química 68



Passo 1 Síntese de 4-(3-cloro-4-(3-fluorobenziloxi)fenilamino)-6-(1-hidroxietan-1-il)quinazolina (VI-1)

Em 30 mL de tetra-hidrofurano foi dissolvido 620 mg de 4-(3-cloro-4-(3-fluorobenziloxi)fenilamino)-6-formil-quinazolina

(IV-1), a solução foi arrefecida até 0 °C sob atmosfera de azoto e foram adicionados, gota a gota, 4,9 mL de brometo de metilmagnésio (solução 0,93 M em tetra-hidrofurano). Após reacção a 0 °C durante 1 hora sob atmosfera de azoto, foram adicionados água e acetato de etilo para separar as camadas. A camada orgânica foi lavada sequencialmente com água e solução aquosa saturada de cloreto de sódio, e seca sobre sulfato de magnésio. Após concentração, o cristal resultante foi lavado com clorofórmio para obter 330 mg de 4-(3-cloro-4-(3-fluorobenziloxi)fenilamino)-6-(1-hidroxietan-1-il)quinazolina (VI-1).

RMN de ^{1}H (d_6-DMSO, δ): 9,81 (1H, s), 8,55 (1H, s), 8,44 (1H, s), 8,03 (1H, d, J = 2,4 Hz), 7,86 (1H, dd, J = 8,7 Hz, J = 1,2 Hz), 7,78-7,73 (2H, m), 7,51-7,44 (1H, m), 7,35-7,25 (3H, m), 7,18 (1H, dt, J = 8,4 Hz, J = 2,4 Hz), 5,44 (1H, d, J = 3,9 Hz), 5,26 (2H, s), 4,93 (1H, m), 1,45 (3H, d, J = 6,6 Hz)

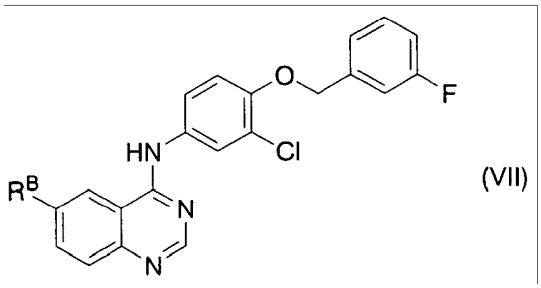
Passo 2 Síntese de 4-(3-cloro-4-(3-fluorobenziloxi)fenilamino)-6-(etano-4-ona)quinazolina (VII-1)

Em 150mL de tetra-hidrofurano foi dissolvido 360 mg de 4-(3-cloro-4-(3-fluorobenziloxi)fenilamino-6-(1-hidroxietan-1-il)quinazolina (VI-1) e foi adicionado 3,7 g de dióxido de manganês, seguido de agitação à temperatura ambiente de um dia para o outro. Após a reacção, as substâncias inorgânicas foram filtradas e o filtrado foi concentrado. O cristal resultante foi lavado com clorofórmio para obter 320 mg de 4-(3-cloro-4-(3-fluorobenziloxi)fenilamino)-6-(etano-4-ona)quinazolina (VII-1).

RMN de ^{1}H (d_6-DMSO, δ): 10,18 (1H, s), 9,16 (1H, d, J = 1,5 Hz), 8,64 (1H, s), 8,31 (1H, dd, J = 8,4 Hz, J = 2,4 Hz), 7,97 (1H, d, J = 2,4 Hz), 7,83 (1H, d, J = 8,7 Hz), 7,71 (1H, dd, J = 8,7 Hz, J = 2,4 Hz), 7,51-7,44 (1H, m), 7,35-7,29 (3H, m), 7,19 (1H, dt, J = 8,1 Hz, J = 2,7 Hz), 5,27 (2H, s), 2,74 (3H, s)

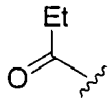
Os compostos seguintes foram sintetizados de acordo com o mesmo modo que o do primeiro passo acima e segundo passo.

Fórmula química 69

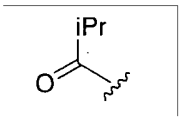
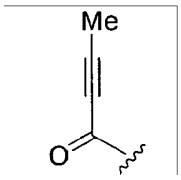
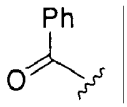
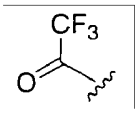
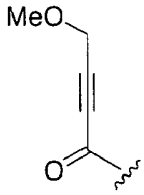
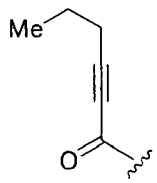


(VII)

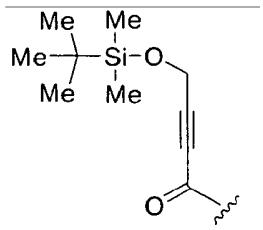
Quadro 12

N° do Composto	R^B	RMN de ^{1}H (d_6-DMSO)
VII-2		10,17(1H, s), 9,17(1H, d, J = 1,5 Hz), 8,64(1H, s), 8,32(1H, dd, J = 8,7 Hz, J = 1,5 Hz), 7,97(1H, d, J = 2,7 Hz), 7,84(1H, d, J = 8,7 Hz), 7,72(1H, dd, J = 8,7 Hz, J = 2,7 Hz), 7,52-7,44(1H, m), 7,35-7,29(3H, m), 7,20(1H, dt, J = 8,7 Hz, J = 2,7 Hz), 5,28(2H, s), 3,22(2H, q, J = 7,2 Hz), 1,17(3H, t, J = 7,2 Hz)

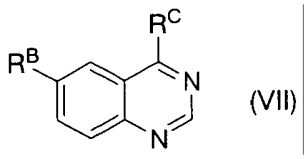
(continuação)

Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VII-3		($CDCl_3$) 8,76(1H, s), 8,65(1H, s l), 8,29(1H, d, J = 9,0 Hz), 7,97(1H, d, J = 8,4 Hz), 7,88(1H, s l), 7,52(1H, d, J = 9,0 Hz), 7,40-7,33(1H, m), 7,25-7,19(3H, m), 7,05-6,97(2H, m), 5,16(2H, s), 3,72-3,63(1H, m), 1,28(3H, d, J = 1,8 Hz), 1,26(3H, d, J = 1,8 Hz)
VII-4		10,34(1H, s), 9,23(1H, s), 8,66(1H, s), 8,44(1H, dd, J = 9 Hz, J = 1,5 Hz), 7,99(1H, d, J = 2,7 Hz), 7,88(1H, d, J = 8,7 Hz), 7,72(1H, dd, J = 9 Hz, J = 2,4 Hz), 7,43-7,52(1H, m), 7,14-7,36(4H, m), 5,28(2H, s), 2,28(3H, s)
VII-5		10,14(1H, s), 8,98(1H, s), 8,67(1H, s), 8,11(1H, dd, J = 8,7 Hz, J = 0,9 Hz), 7,98-7,82(4H, m), 7,78-7,58(4H, m), 7,52-7,43(1H, m), 7,36-7,14(4H, m), 5,26(2H, s)
VII-6		10,50(1H, s), 9,27(1H, s), 8,67(1H, s), 8,35(1H, d, J = 9,3 Hz), 7,99(1H, d, J = 2,7 Hz), 7,88(1H, s l), 7,70(1H, d, J = 7,5 Hz), 7,52-7,43(1H, m), 7,36-7,14(4H, m), 5,28(2H, s)
VII-8		10,36(1H, s), 9,26(1H, s), 8,67(1H, s), 8,44(1H, dd, J = 8,7 Hz, J = 1,8 Hz), 8,00(1H, d, J = 2,4 Hz), 7,91(1H, d, J = 8,7 Hz), 7,72(1H, dd, J = 9,0 Hz, J = 2,4 Hz), 7,51-7,44(1H, m), 7,35-7,28(3H, m), 7,22-7,15(1H, m), 5,27(2H, s), 4,55(2H, s).
VII-9		10,4(1H, s), 9,24(1H, s), 8,67(1H, s), 8,46(1H, d, J = 8,7 Hz), 8,01(1H, d, J = 2,7 Hz), 7,90(1H, d, J = 8,7 Hz), 7,70-7,80(1H, m), 7,44- 7,54(1H, m), 7,15-7,40(4H, m), 5,27(2H, s), 2,64(2H, t, J = 6,9 Hz), 1,63-1,75(2H, m), 1,05(3H, t, J = 7,5 Hz)

(continuação)

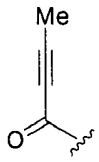
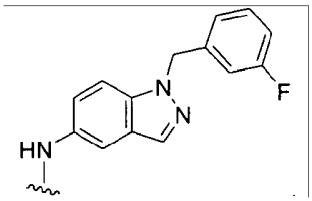
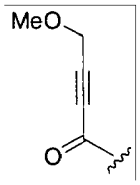
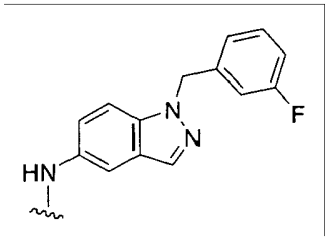
Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VII-10		10,34(1H, s), 9,24(1H, s), 8,67(1H, s), 8,42(1H, d, J = 8,4 Hz), 7,99(1H, s), 7,88(1H, d, J = 8,7 Hz), 7,73(1H, d, J = 9,0 Hz), 7,48-7,44(1H, m), 7,34-7,27(3H, m), 7,21-7,16(1H, m), 5,27(2H, s), 4,76(2H, s), 0,94(9H, s), 0,16(6H, s).

Fórmula química 70

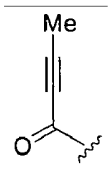
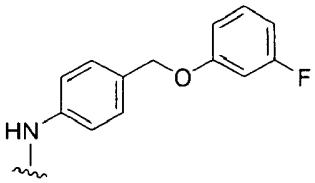
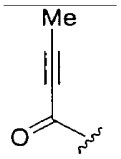
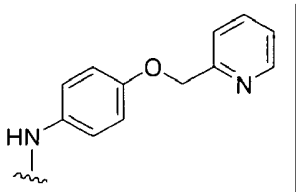
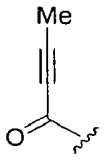
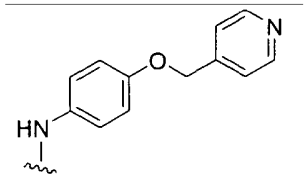
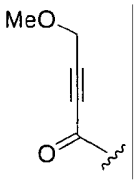
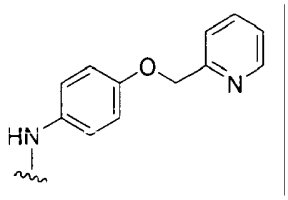


(VII)

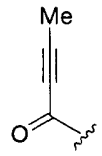
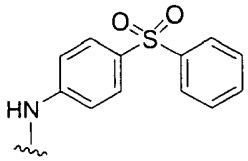
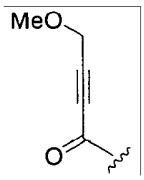
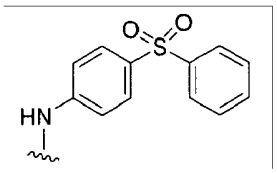
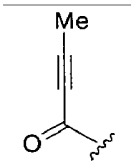
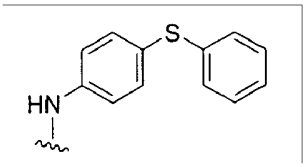
Quadro 13

Nº do Composto	R^B	R^C	RMN de ^1H (d_6-DMSO)
VII-11			10,44(1H, s), 9,24(1H, s), 8,60(1H, s), 8,43(1H, dd, J = 2,4, 11,6 Hz), 8,17(2H, s), 7,87(1H, d, J = 12,0 Hz), 7,78-7,67(2H, m), 7,41-7,34(1H, m), 7,14-7,04(3H, m), 5,72(2H, s), 2,28(3H, s)
VII-12			10-47(1H, s), 9,29(1H, d, J = 1,8 Hz), 8,62(1H, s), 8,43(1H, dd, J = 1,5 Hz, J = 9,0 Hz), 8,21-8,17(2H, m), 7,89(1H, d, J = 8,7 Hz), 7,78-7,68(2H, m), 7,41-7,33(1H, m), 7,15-7,04(3H, m), 5,71(2H, s), 4,55(2H, s), 3,42(3H, s).

(continuação)

Nº do Composto	R^B	R^C	RMN de ^1H (d_6-DMSO)
VII-13			10,44(1H, s), 9,25(1H, s), 8,73(1H, s), 8,44(1H, d, J = 8,8 Hz), 8,16(1H, s), 7,89(1H, d, J = 8,4 Hz), 7,62(1H, d, J = 8,4 Hz), 7,34(1H, dd, J = 8,4, 16.O Hz), 6,95-6,86(2H, m), 6,82-6,77(1H, m), 5,15(2H, s), 2,27(3H, s).
VII-14			10,34(1H, s), 9,22(1H, s), 8,64-8,59(2H, m), 8,43-8,41(1H, m), 7,98(1H, s), 7,87-7,85(2H, m), 7,71-7,68(1H, m), 7,59-7,58(1H,m), 7,40-7,34(1H, m), 7,29-7,27(1H, m), 5,30(2H, s).
VII-15			9,21(1H, s), 8,64-8,58(2H, m), 8,45-8,39(1H, m), 7,97(1H, s), 7,88-7,84(1H, m), 7,71-7,66(1H, m), 7,45-7,51(1H,m), 7,27-7,23(1H, m), 7,29-7,27(1H, m), 5,30(2H, s).
VII-16			10,35(1H, s), 9,24(1H, s), 8,67(1H, s), 8,60(1H, d, J = 4,4 Hz), 8,42(1H, d, J = 8,8 Hz), 8,01(1H, s), 7,91-7,87(2H, m), 7,73-7,71(1H, m), 7,59(1H, d, J = 8,0 Hz), 7,39-7,36(1H, m), 7,29(1H, d, J = 8,8 Hz), 5,31(2H, s), 4,55(2H, s), 3,42(3H, s).

Quadro 14

Nº do Composto	R^B	R^C	RMN de ^1H (d_6-DMSO)
VII-17			10,32 (1H, s), 8,85(1H, s), 8,74(1H, s), 8,20(2H, d, J = 6,0 Hz), 8,01-7,96(4H, m), 7,87(1H, d, J = 6,0 Hz), 7,68-7,64 (3H, m), 3,56(3H, s).
VII-18			10,52(1H, s), 9,14(1H, s), 8,60(1H, s), 8,31(1H, d, J = 8,4 Hz), 8,40(2H, d, J = 8,4 Hz), 7,84-7,78(5H, m), 7,52-7,43(3H, m), 4,37(2H, s), 3,24(3H, s).
VII-19			10,44(1H, s), 9,28(1H, s), 8,70(1H, s), 8,45(1H, d, J = 8,8 Hz), 7,92(3H, t, J = 8,8 Hz), 7,46(2H, d, J = 8,8 Hz), 7,37 (2H, t, J = 7,6 Hz), 7,30-7,26(3H, m), 4,24-4,20(2H, m), 2,28 (3H, s).

Passo 3 Síntese de 4-(3-cloro-4-(3-fluorobenziloxi)fenilamino)-6-(1-(2-(1-morfolino)etoxiimino)etil)quinazolina (VIII-1)

Em 6 mL (20:1) de uma mistura de tetra-hidrofurano e água foram dissolvidos 100 mg de Composto VII-1 e 78 mg de dicloridrato de 2-(1-morfolino)etoxiamina, seguido de agitação à temperatura ambiente de um dia para o outro. A mistura reaccional foi diluída com acetato de etilo, lavada com solução aquosa saturada de bicarbonato de sódio e seca sobre sulfato de magnésio. Após concentração, o sólido foi lavado com uma mistura (2:1) de hexano e acetato de etilo para obter 72 mg de

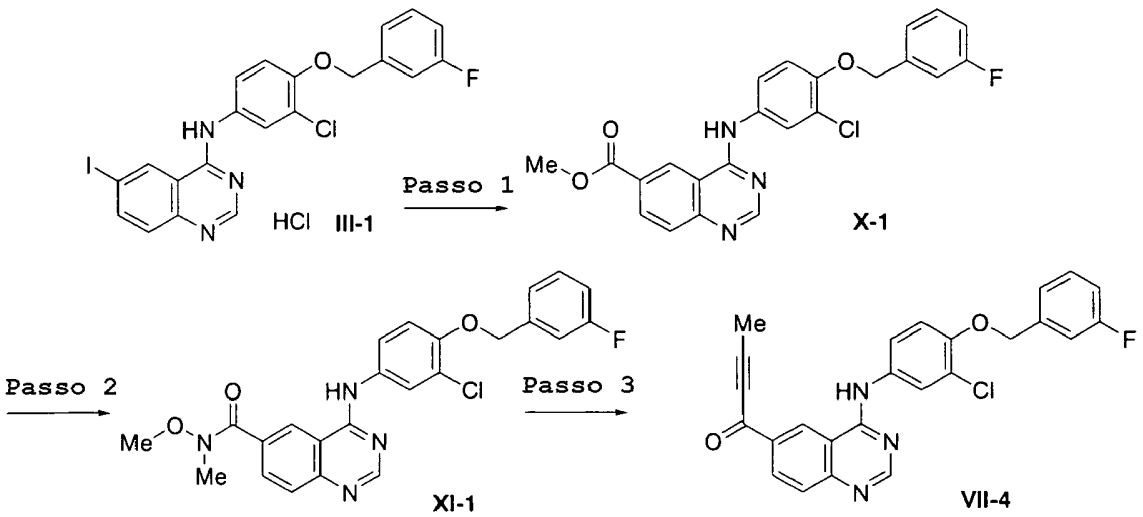
4-(3-cloro-4-(3-fluorobenziloxi)fenilamino)-6-(1-(2-(1-morfolino)etoxiimino)etil)quinazolina (VIII-1).

RMN de ^{1}H (d_6-DMSO, δ): 9,93 (1H, s), 8,62 (1H, s l), 8,58 (1H, s), 8,22 (1H, d, J = 6,6 Hz), 7,96 (1H, d, J = 1,8 Hz), 7,76 (1H, d, J = 6,6 Hz), 7,70 (1H, dd, J = 6,6 Hz, J = 1,8 Hz), 7,51-7,45 (1H, m), 7,35-7,28 (3H, m), 7,19 (1H, t, J = 6,0 Hz), 5,27 (2H, s), 4,33 (2H, t, J = 6,0 Hz), 3,59 (4H, t, J = 4,5 Hz), 2,69 (2H, t, J = 6,0 Hz), 2,47 (4H, t, J = 4,5 Hz), 2,36 (3H, s)

Exemplo de Referência 1

Como um método de obter uma derivado de cetona (VII) é exemplificado o método seguinte além do primeiro passo e do segundo passo do Exemplo 7.

Fórmula química 71



Passo 1 Síntese de éster metílico do ácido 4-(3-cloro-4-(3-fluorobenziloxi)fenilamino)-quinazolina-6-carboxílico (X-1)

Numa mistura de 200 mL de dimetilformamida e 200 mL de metanol foram dissolvidos cloridrato de 4-(3-cloro-4-(3-fluorobenziloxi)fenilamino)-6-iodoquinazolina (III-1, 20 g) e 1,29 g de diclorobis(trifenilfosfina)paládio, e foram adicionados 25,7 mL de trietilamina. O interior de um recipiente reaccional foi suficientemente substituído com monóxido de carbono gasoso, seguido de uma reacção a 80 °C durante 15 horas sob atmosfera de monóxido de carbono. A mistura reaccional foi filtrada com Celite e o filtrado foi arrefecido até 0 °C sob agitação. Foi filtrado um precipitado, lavado com metanol frio e seco para obter éster metílico do ácido 4-(3-cloro-4-(3-fluorobenziloxi)fenilamino)quinazolina-6-carboxílico (X-1, 13,5 g) como um sólido incolor.

RMN de ^{1}H (d_6-DMSO, δ): 10,26 (1H, s), 9,25 (1H, d, J = 1,5 Hz), 8,65 (1H, s), 8,31 (1H, dd, J = 1,5 Hz, J = 8,7 Hz), 8,02 (1H, d, J = 2,7 Hz), 7,85 (1H, d, J = 2,7 Hz), 7,77 (1H, dd, J = 2,7 Hz, J = 8,7 Hz), 7,49-7,44 (1H, m), 7,35-7,27 (3H, m), 7,20-7,16 (1H, m), 5,27 (2H, s), 3,96 (3H, s).

Passo 2 Síntese de metoximetilamida do ácido 4-(3-cloro-4-(3-fluorobenziloxi)fenilamino)quinazolina-6-carboxílico (XI-1)

Em tetra-hidrofurano (230 mL) foi dissolvido éster metílico do ácido 4-(3-cloro-4-(3-fluorobenziloxi)fenilamino)-quinazolina-6-carboxílico (X-1, 11,6 g), foi adicionado cloridrato de N,O-dimetil-hidroxilamina (7,8 g) e foi adicionada, gota a gota ao longo de 30 minutos sob arrefecimento

com gelo, solução de iPrMgCl 2 mol/L em tetra-hidrofurano (79,8 mL). Depois de a adição estar completa, a mistura foi agitada durante 20 minutos sob arrefecimento com gelo e, depois de a reacção estar completa, foram adicionados 200 mL de solução aquosa saturada de cloreto de amónio. Depois de terem sido adicionados 100 mL de água à mistura, a mistura foi extraída com acetato de etilo e a camada orgânica foi seca sobre sulfato de sódio. O filtrado foi concentrado para obter metoximetilamida do ácido 4-(3-cloro-4-(3-fluorobenziloxi)fenilamino)-quinazolina-6-carboxílico (XI-1, 12,7 g) como um sólido amarelo pálido.

RMN de ^{1}H (d_6-DMSO, δ): 10,01 (1H, s), 8,79 (1H, d, J = 1,5 Hz), 8,64 (1H, s), 8,05 (1H, d, J = 2,7 Hz), 8,00 (1H, dd, J = 1,5 Hz, J = 8,7 Hz), 7,81 (1H, d, J = 8,7 Hz), 7,76 (1H, dd, J = 2,7 Hz, J = 8. 7 Hz); 7,52-7,44 (1H, m), 7,35-7,26 (3H, m), 7,22-7,16 (1H, m), 5,27 (2H, s), 3,57 (3H, s), 3,34 (3H, s).

Passo 3 Síntese de 4-(3-cloro-4-(3-fluorobenziloxi)fenilamino)-6-(1-oxo-2-butin-1-il)quinazolina (VII-4)

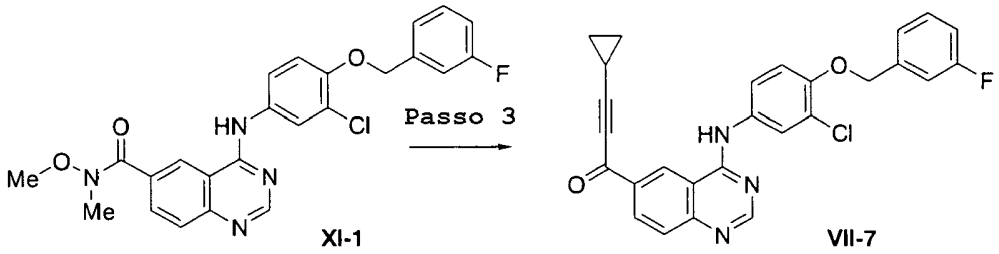
A uma solução de 4,22 mL de N,N-diisopropilamina em tetra-hidrofurano (25 mL) arrefecida até -78 °C foram adicionados, gota a gota, 18,8 mL de solução de n-BuLi 1,6 mol/L em hexano. Depois de a adição estar completa, a temperatura foi aumentada até 0 °C e a mistura foi agitada a 0 °C durante 20 minutos, e novamente arrefecida até -78 °C. Foram adicionados 1,33 mL de 2-bromo-1-propeno em tetra-hidrofurano (25 mL) e a mistura foi agitada a -78 °C durante 2 horas. À mistura foi adicionada gota a gota uma solução de metoximetilamida do ácido 4-(3-cloro-4-(3-fluorobenziloxi)fenilamino)-quinazolina-6-

carboxílico (XI-1, 2,33 g) em tetra-hidrofurano (50 mL) e, depois de a adição estar completa, a temperatura foi aumentada até 0 °C, seguido de agitação durante 3 horas. Depois de a reacção estar completa, a mistura reaccional foi vertida para água gelada, neutralizada com ácido clorídrico 2 mol/L e extraída com acetato de etilo. A camada orgânica foi seca sobre sulfato de sódio, o filtrado foi concentrado e o resíduo cristalino resultante foi lavado com cloreto de metileno para obter 4-(3-cloro-4-(3-fluorobenziloxi)fenilamino)-6-(1-oxo-2-butin-1-il)quinazolina (VII-4, 1,71 g) como um sólido amarelo.

Exemplo de Referência 2

Como outro método do terceiro passo do Exemplo de Referência 1, há o método seguinte.

Fórmula química 72



Passo 3 Síntese de 4-(3-cloro-4-(3-fluorobenziloxi)fenilamino)-6-(1-oxo-2-propino-3-ciclopropil-1-il)quinazolina (VII-7)

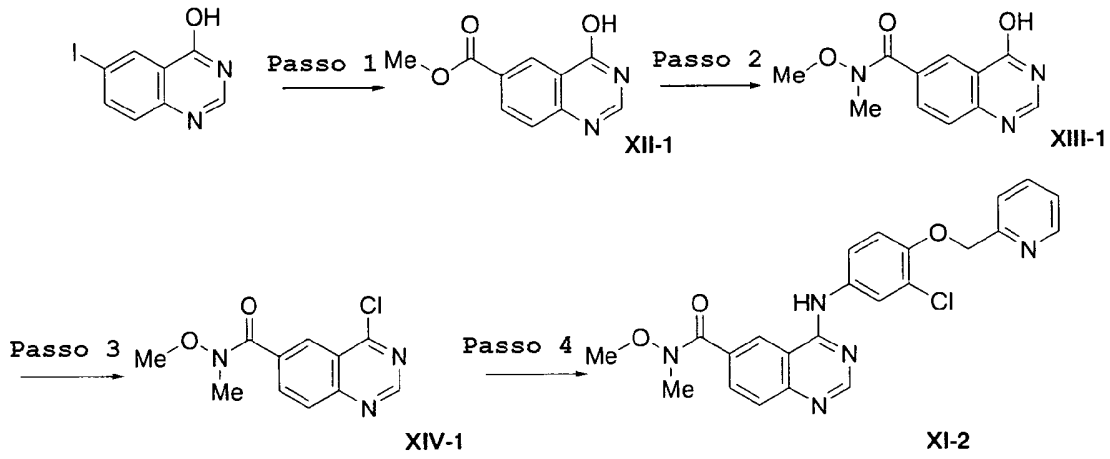
A uma solução de 0,16 mL de etinilciclopropano em tetra-hidrofurano (3 mL) arrefecido até -78 °C foram adicionados, gota a gota, 1,25 mL de solução de n-BuLi 1,54 mol/L em hexano. Depois de a adição estar completa, a mistura foi agitada a -78 °C durante 1 hora. À mistura foi adicionada gota a gota uma solução de metoximetilamida do ácido 4-(3-cloro-4-(3-fluorobenziloxi)fenilamino)-quinazolina-6-carboxílico (XI-1, 300 mg) em tetra-hidrofurano (3 mL) e, depois de a adição estar completa, a temperatura foi aumentada até 0 °C e a mistura foi agitada durante 3 horas. Depois de a reacção estar completa, foram adicionados 10 mL de água e 10 mL de acetato de etilo à mistura reaccional para separar as camadas. Depois de a camada aquosa ter sido reextraída duas vezes com 10 mL de acetato de etilo, todas as camadas orgânicas foram combinadas e secas sobre sulfato de sódio, e o filtrado foi concentrado. O resíduo foi purificado por cromatografia em coluna sobre sílica gel para obter 4-(3-cloro-4-(3-fluorobenziloxi)fenilamino)-6-(1-oxo-2-propino-3-ciclopropil-1-il)quinazolina) (VII-7, 265 mg) como um sólido amarelo.

RMN de ^{1}H (d_6-DMSO, δ): 10,4 (1H, s), 9,21 (1H, s), 8,67 (1H, s), 8,41 (1H, d, J = 8,7 Hz), 8,01 (1H, d, J = 2,7 Hz), 7,88 (1H, d, J = 8,7 Hz), 7,73 (1H, dd, J = 8,7 Hz, J = 3 Hz), 7,40-7,52 (1H, m), 7,15-7,4 (4H, m), 5,28 (2H, s), 1,77-1,87 (1H, m), 1,05-1,20 (3H, m).

Exemplo de Referência 3

Como um método de obter um derivado de amida (XI), há o método seguinte além do primeiro passo e do segundo passo do Exemplo de Referência 1.

Fórmula química 73



Passo 1 Síntese de éster metílico do ácido 4-hidroxiquinazolina-6-carboxílico (XII-1)

4-Hidroxi-6-iodoquinazolina (250 mg), uma quantidade catalítica de acetato de paládio (II) e 1,3-bis(difenilfosfino)propano foram dissolvidos em N,N-dimetilformamida (3,8 mL) e foram adicionados metanol (1,5 mL) e 1,5 mL de trietilamina. Depois de o interior de um recipiente reaccional ter sido suficientemente substituído com monóxido de carbono gasoso, foi realizada uma reacção a 80 °C durante 20 horas sob atmosfera de monóxido de carbono. Depois de a reacção estar completa, a mistura reaccional foi vertida para ácido cítrico aquoso a 10%, seguida de extracção com acetato de

etilo. A camada orgânica foi lavada com água e seca sobre sulfato de sódio, e o filtrado foi concentrado. O resíduo resultante foi purificado por cromatografia em coluna sobre sílica gel (eluindo com acetato de etilo) para obter éster metílico do ácido 4-hidroxiquinazolina-6-carboxílico (XII-1, 157 mg) como um sólido castanho.

RMN de ^{1}H (d_6-DMSO, δ): 12,48 (1H, s), 8,63 (1H, s), 8,26 (1H, d, J = 8,4 Hz), 8,19 (1H, s), 7,73 (1H, d, J = 8,4 Hz).

Passo 2 Síntese de metoximetilamida do ácido 4-hidroxiquinazolina-6-carboxílico (XIII-1)

Éster metílico do ácido 4-hidroxiquinazolina-6-carboxílico (XII-1, 4,0 g) foi dissolvido em tetra-hidrofurano (120 mL), foi adicionado cloridrato de N,O-dimetil-hidroxilamina (5,7 g) e foi adicionada, gota a gota, ao longo de 30 minutos, solução de iPrMgCl 2 mol/L em tetra-hidrofurano (59 mL). Depois de a adição estar completa, a mistura foi agitada durante 30 minutos sob arrefecimento com gelo e, depois de a reacção estar completa, foram adicionados, gota a gota, 40 mL de ácido clorídrico 2 mol/L. A mistura foi neutralizada com solução aquosa saturada de bicarbonato de sódio e extraída com clorofórmio, e a camada orgânica foi lavada com solução aquosa de cloreto de sódio, e seca sobre sulfato de sódio. Após concentração, o resíduo cristalino foi purificado por cromatografia em coluna sobre sílica gel (eluindo acetato de etilo: metanol = 9:1) para obter metoximetilamida do ácido 4-hidroxiquinazolina-6-carboxílico (XIII-1, 2,9 g) como um sólido branco.

RMN de ^{1}H (d_6-DMSO, δ): 12,42 (1H, s), 8,36 (1H, s), 8,18 (1H, s), 8,02 (1H, d, J = 8,4 Hz), 7,73 (1H, d, J = 8,4 Hz), 3,57 (3H, s), 3,32 (3H, s).

Passo 3 Síntese de metoximetilamida do ácido 4-cloroquinazolina-6-carboxílico (XIV-1)

Metoximetilamida do ácido 4-hidroxiquinazolina-6-carboxílico (XIII-1, 2,9 g) foi suspensa em tolueno (57 mL), e foram adicionados 6,8 mL de trietilamina e 3,4 mL de oxicloreto de fósforo, seguido de agitação a 130 °C durante 30 minutos. Depois de a reacção estar completa, a mistura reaccional foi arrefecida até à temperatura ambiente e foram adicionados 50 mL de solução aquosa saturada de bicarbonato de sódio e acetato de etilo. Foi adicionado bicarbonato de sódio até a camada aquosa exibir um pH de 8, seguida de extracção com acetato de etilo. A camada orgânica foi lavada com solução aquosa saturada de bicarbonato de sódio, seca sobre sulfato de sódio. Após concentração, o resíduo cristalino foi lavado com éter dietílico e seco para obter metoximetilamida do ácido 4-cloroquinazolina-6-carboxílico (XIV-1, 2,3 g) como um sólido branco.

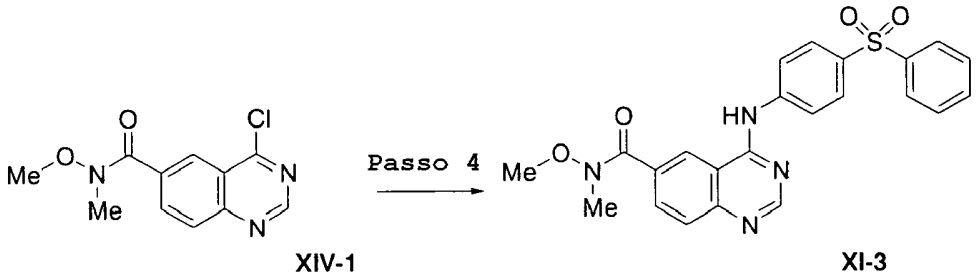
RMN de ^{1}H (d_6-DMSO, δ): 8,75 (1H, s), 8,36 (1H, s), 8,11 (1H, dd, J = 2,0 Hz, J = 8,4 Hz), 7,87 (1H, d, J = 8,4 Hz), 3,56 (3H, s), 3,32 (3H, s).

Passo 4 Síntese de metoximetilamida do ácido 4-(3-cloro-4-(piridin-2-ilmetoxi)fenilamino)-quinazolina-6-carboxílico (XI-2)

Metoximetilamida do ácido 4-cloroquinazolina-6-carboxílico (XIV-1, 5,78 g) foi dissolvida em tetra-hidrofurano (100 mL), e foi adicionado 5,39 g de 3-cloro-4-(piridin-2-ilmetoxi)anilina, seguido de agitação a 60 °C durante 1 hora. Foi filtrado um precipitado e lavado com tetra-hidrofurano para obter metoximetilamida do ácido 4-(3-cloro-4-(piridin-2-ilmetoxi)fenilamino)-quinazolina-6-carboxílico (XI-2, 7,87 g) como um sólido branco. O filtrado foi deixado em repouso à temperatura ambiente e o precipitado resultante foi recolhido por filtração, to obter de novo 2,21 g de XI-2.

RMN de ^{1}H (d_6-DMSO, δ): 10,02 (1H, s), 8,79 (1H, s), 8,62-8,59 (2H, m), 8,04 (1H, s), 8,00-7,98 (1H, m), 7,90-7,86 (1H, s), 7,80-7,78 (1H, m), 7,75-7,73 (1H, m), 7,59-7,57 (1H, m), 7,37-7,35 (1H, m), 7,28-7,26 (1H, m), 5,29 (2H, s), 3,57 (3H, s).

Fórmula química 74



XIV-1 XI-3

Exemplo de Referência 4

Como outro método do quarto passo do Exemplo de Referência 3, há o método seguinte.

Passo 4 Síntese de metoximetilamida do ácido 4-(4-benzenossulfonilfenilamino)-quinazolina-6-carboxílico (XI-3)

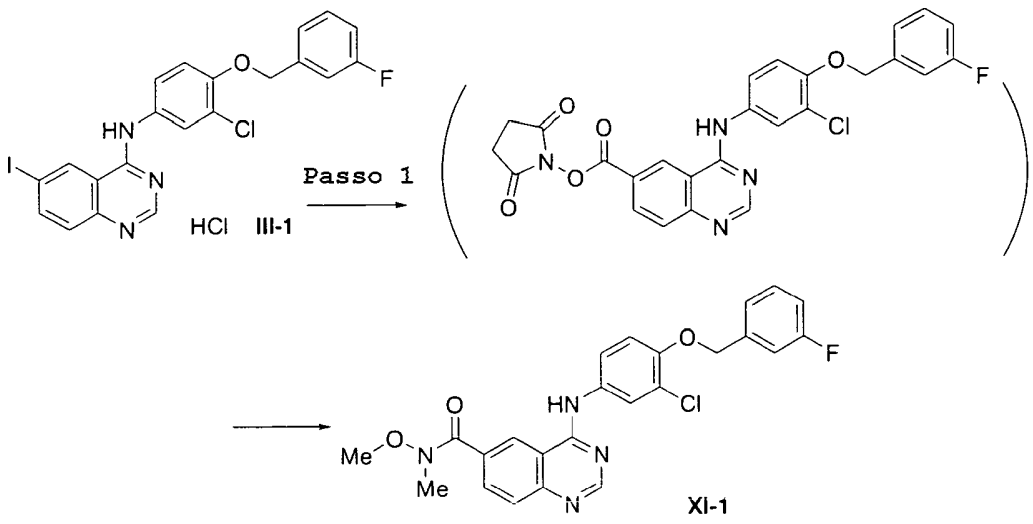
Foram adicionados metoximetilamida do ácido 4-cloroquinazolina-6-carboxílico (XIV-1, 550 mg), 611 mg de 4-benzenossulfonilfenilamina, 49 mg de acetato de paládio (II), 190 mg de Xantphos e 997 mg de carbonato de césio a 1,4-dioxano (30 mL), e o interior de um recipiente reaccional foi substituído por azoto gasoso, seguido de agitação a 100 °C durante 2,5 horas. A mistura reaccional foi filtrada com Celite e foi adicionada água ao filtrado, seguida de extracção com acetato de etilo. A camada orgânica foi lavada com solução aquosa saturada de cloreto de sódio e seca sobre sulfato de sódio. O filtrado foi concentrado e o resíduo foi purificado por cromatografia em coluna sobre sílica gel (eluindo com acetato de etilo: metanol = 95:5) para obter metoximetilamida do ácido 4-(4-benzenossulfonilfenilamino)-quinazolina-6-carboxílico (XI-3, 651 mg) como um sólido amarelo pálido.

RMN de ^{1}H (d_6-DMSO, δ): 10,66 (1H, s), 9,29 (1H, s), 8,80 (1H, s), 8,48 (1H, d, J = 7,7 Hz), 8,16 (2H, d, J = 7,7 Hz), 7,99-7,94 (5H, m), 7,80-7,61 (3H, m), 2,27 (3H, s).

Exemplo de Referência 5

Como um método de obter um derivado de amida (XI), há ainda o método seguinte além do primeiro passo e do segundo passo do Exemplo de Referência 1 e Exemplo de Referência 3.

Fórmula química 75



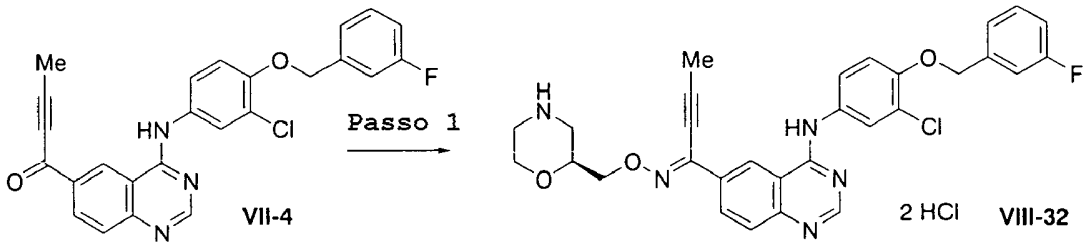
Passo 1 Síntese de metoximetilamida do ácido 4-(3-cloro-4-(3-fluorobenziloxi)fenilamino)-quinazolina-6-carboxílico (XI-1)

Cloridrato de 4-(3-cloro-4-((3-fluorobenziloxi)fenilamino)-6-iodoquinazolina (III-1, 500 mg), 32 mg de diclorobis(trifenilfosfina)paládio e 191 mg de N-hidroxissuccinimida foram dissolvidos em 10 mL de dimetilformamida e foram adicionados 360 µL de trietilamida. O interior de um recipiente reaccional foi suficientemente substituído com monóxido de carbono gasoso, seguida de uma reacção a 80 °C durante 3 horas sob atmosfera de monóxido de

carbono. A 1/5 da mistura reaccional foram adicionados 0,3 mL de uma solução aquosa de N,O-dimetil-hidroxilamina a 40%, seguido de agitação à temperatura ambiente de um dia para o outro. Depois de a reacção estar completa, foi adicionada água à mistura reaccional, seguida de extracção com acetato de etilo. A camada orgânica foi lavada com água e solução aquosa saturada de cloreto de sódio por esta ordem, e seca sobre sulfato de sódio. O resíduo concentrado do filtrado foi purificado por cromatografia em coluna sobre sílica gel (eluindo com acetato de etilo) para obter metoximetilamida do ácido 4-(3-cloro-4-(3-fluorobenziloxi)fenilamino)-quinazolina-6-carboxílico (XI-1, 74 mg) como um sólido amarelo pálido.

Exemplo 8

Fórmula química 76



Passo 1 Síntese de dicloridrato de 4-(3-cloro-4-(3-fluorobenziloxi)fenilamino)-6-(1-((S)-morfolin-2-ilmetoxiimino)-2-butin-1-il)quinazolina (VIII-32)

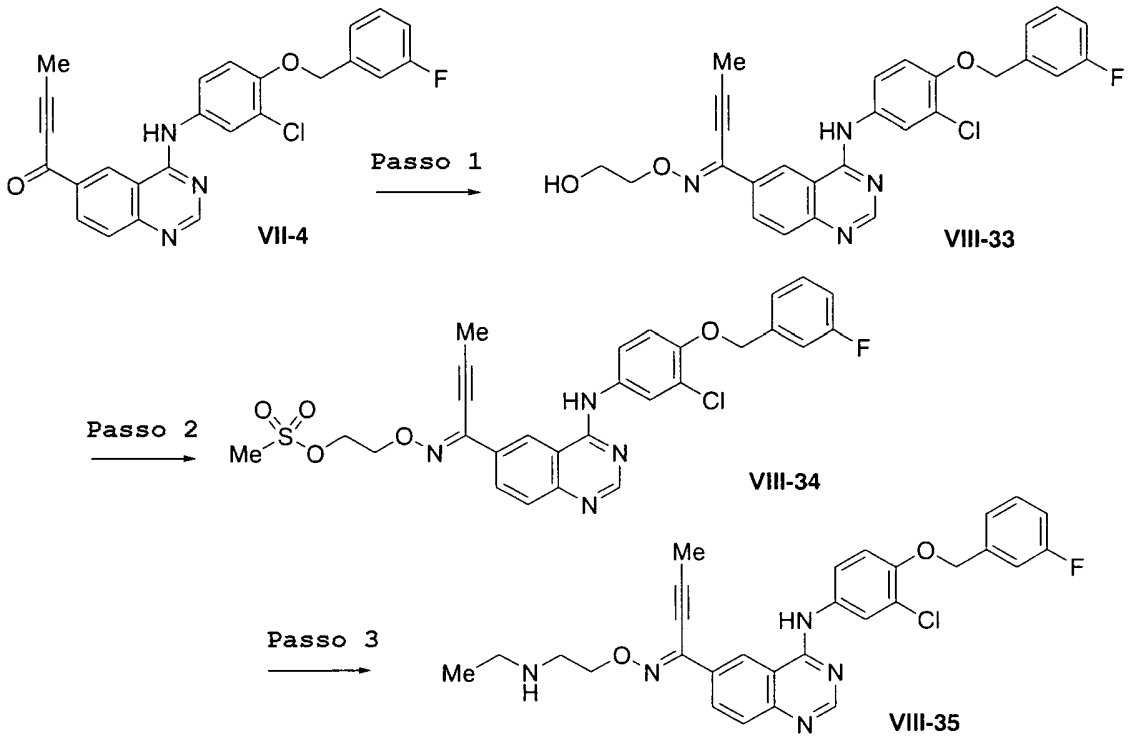
A uma suspensão de 4-(3-cloro-4-(3-fluorobenziloxi)fenilamino)-6-(1-oxo-2-butin-1-il)quinazolina (VII-4, 786 mg) e 614 mg de éster terc-butílico do ácido

(S)-2-aminooximetil-morfolina-4-carboxílico em 31 mL de 1,4-dioxano foram adicionados 2,21 mL de solução aquosa de ácido metanossulfónico a 2 mol/L, seguido de agitação a 80 °C durante 22 horas. E foram adicionalmente adicionados 1,32 mL de solução aquosa de ácido metanossulfónico 2 mol/L, seguida de agitação durante mais 5,5 horas. Depois de a reacção estar completa, a mistura reaccional foi vertida para solução aquosa de bicarbonato de sódio, seguida de extracção com acetato de etilo. Depois de a camada aquosa ter sido reextraída com acetato de etilo, todas as camadas orgânicas foram combinadas, lavadas com água e secas sobre sulfato de magnésio anidro. Depois de o filtrado ter sido concentrado, o resíduo foi purificado por cromatografia em coluna sobre sílica gel (eluindo com clorofórmio: metanol = 9:1) para obter um óleo amarelo. Este óleo foi dissolvido em 50 mL de acetato de etilo, e filtrado, e foram adicionados 0,95 mL de solução de ácido clorídrico 4 mol/L-acetato de etilo sob agitação, seguido de agitação à temperatura ambiente durante 1 hora. Foi filtrado um precipitado, e lavado com acetato de etilo e hexano por esta ordem. Uma substância recolhida por filtração foi recristalizada com metanol-acetato de etilo para obter dicloridrato de 4-(3-cloro-4-(3-fluorobenziloxi)fenilamino)-6-(1-((S)-morfolin-2-ilmetoxiimino)-2-butin-1-il)quinazolina (VIII-32, 839 mg) como um cristal amarelo.

RMN de ^{1}H (d_6-DMSO, δ): 11,69 (1H, sl), 9,49-9,37 (2H, m), 9,05 (1H, s), 8,88 (1H, s), 8,38 (1H, dd, J = 1,5 Hz, J = 8,7 Hz), 7,96 (1H, d, J = 8,7 Hz), 7,89 (1H, d, J = 2,7 Hz), 7,64 (1H, dd, J = 2,4 Hz, J = 9,0 Hz), 7,52-7,45 (1H, m), 7,36-7,30 (3H, m), 7,23-7,16 (1H, m), 5,31 (2H, s), 4,36-4,34 (1H, m), 4,25-4,22 (1H, m), 4,04-3,98 (1H, m), 3,84-3,77 (1H, m), 3,04-2,85 (3H, m), 2,28 (3H, s).

Exemplo 9

Fórmula química 77



Passo 1 Síntese de 4-(3-cloro-4-(3-fluorobenziloxi)fenilamino)-6-(1-(2-hidroxietoxiimino)-2-butin-1-il)quinazolina (VIII-33)

4-(3-Cloro-4-(3-fluorobenziloxi)fenilamino)-6-(1-oxo-2-butin-1-il)quinazolina (VII-4, 10 g) foi dissolvida em 300 mL de 1,4-dioxano, foram adicionados 1,5 equivalentes de 2-(acetoxi)etoxiamina e foram adicionados 28 mL de solução aquosa de ácido metanossulfónico a 2 mol/L, seguido de agitação a 60 °C durante 17 horas. A mistura reaccional foi vertida para solução aquosa saturada de bicarbonato de sódio e a mistura foi extraída com acetato de etilo. A camada orgânica foi lavada com

água e seca sobre sulfato de sódio. O resíduo obtido concentrando o filtrado foi recristalizado de etanol hidratado-água, filtrado e seco para obter 4-(3-cloro-4-(3-fluorobenziloxi)fenilamino)-6-(1-(2-hidroxietoxiimino)-2-butin-1-il)quinazolina (VIII-33, 7,6 g) como um sólido incolor.

RMN de ^{1}H (d_6-DMSO, δ): 10,07 (1H, s), 8,74 (1H, s), 8,58 (1H, s), 8,22 (1H, d, J = 8,8 Hz), 7,96 (1H, d, J = 2,4 Hz), 7,80 (1H, d, J = 8,8 Hz), 7,69 (1H, dd, J = 2,4 Hz, J = 8,8 Hz), 7,50-7,45 (1H, m), 7,35-7,24 (3H, m), 7,20- 7,16 (1H, m), 5,27 (2H, s), 4,79 (1H, t. J = 5,6 Hz), 4,29 (2H, t. J = 5,6 Hz), 3,75 (2H, dd, J = 5,2 Hz, J = 10,4 Hz), 2,26 (3H, s).

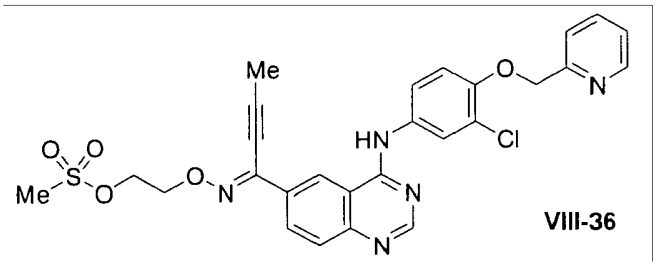
Passo 2 Síntese de 4-(3-cloro-4-(3-fluorobenziloxi)fenilamino)-6-(1-(2-sulfoniloxietoxiimino)-2-butin-1-il)quinazolina (VIII-34)

4-(3-Cloro-4-(3-fluorobenziloxi)fenilamino)-6-(1-(2-hidroxietoxiimino)-2-butin-1-il)quinazolina (VIII-33, 7,6 g) foi dissolvida em 150 mL de tetra-hidrofurano e foram adicionados 4,19 mL de trietilamina e 2,33 mL de cloreto de metanossulfonilo, seguido de agitação durante 3,5 horas. Depois de a reacção estar completa, a mistura reaccional foi vertida para água e foi adicionada solução aquosa saturada de bicarbonato de sódio, seguida de extracção com acetato de etilo. A camada orgânica foi seca sobre sulfato de sódio e o filtrado foi concentrado. Foi adicionado acetato de etilo ao resíduo concentrado, este foi deixado em repouso à temperatura ambiente, precipitou um cristal e foi diluído com hexano, e o cristal foi recolhido por filtração para obter 4-(3-cloro-4-(3-fluorobenziloxi)fenilamino)-6-(1-(2-sulfoniloxietoxiimino)-2-

butin-1-il)quinazolina (VIII-34, 7,66 g) como um cristal amarelo pálido.

RMN de ^{1}H (d_6-DMSO, δ): 10,07 (1H, s), 8,77 (1H, s), 8,60 (1H, s), 8,24 (1H, d, J = 8,8 Hz), 7,97 (1H, d, J = 2,4 Hz), 7,81 (1H, d, J = 8,8 Hz), 7,69 (1H, dd, J = 2,4 Hz, J = 8,8 Hz), 7,51-7,45 (1H, m), 7,35-7,27 (3H, m), 7,21-7,17 (1H, m), 5,27 (2H, s), 4,58 (2H, t. J = 4,8 Hz), 4,54 (2H, t. J = 4,8 Hz), 3,24 (3H, s), 2,27 (3H, s).

Fórmula química 78

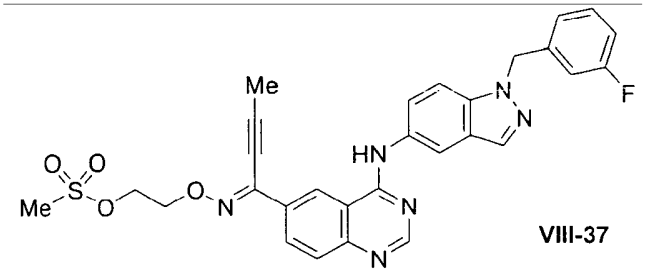


4-(3-Cloro-4-(piridin-2-ilmetoxi)fenilamino)-6-(1-(2-sulfoniloxietoxiimino)-2-butin-1-il)quinazolina (VIII-36)

O composto foi sintetizado de acordo com o mesmo modo que o do primeiro passo e do segundo passo.

RMN de ^{1}H (d_6-DMSO, δ): 10,09 (1H, s), 8,77 (1H, s), 8,61 (1H, s), 8,59 (1H, s), 8,24 (1H, d, J = 8,1 Hz), 7,97 (1H, d, J = 2,4 Hz), 7,89 (1H, t, J = 7,5 Hz), 7,81 (1H, d, J = 9,0 Hz), 7,68 (1H, dd, J = 2,4 Hz, J = 9,0 Hz), 7,59 (1H, d, J = 8,1 Hz), 7,40-7,35 (1H, m), 7,29 (1H, d, J = 9,0 Hz), 5,31 (2H, s), 4,57 (2H, sl), 4,55 (2H, sl), 3,24 (3H, s), 2,27 (3H, s).

Fórmula química 79



VIII-37

4-(1-(3-Fluorobenzil)-1H-indazol-5-ilamino)-6-(1-(2-sulfoniloxietoxiimino)-2-butin-1-il)quinazolina (VIII-37)

O composto foi sintetizado de acordo com o mesmo modo que o do primeiro passo e do segundo passo.

RMN de ^{1}H (d_6-DMSO, δ): 10,20 (1H, s), 8,81 (1H, s), 8,53 (1H, s), 8,24 (1H, d, J = 8,7 Hz), 8,17 (1H, s), 8,13 (1H, s), 7,80 (1H, d, J = 8,7 Hz), 7,75 (1H, d, J = 8,7 Hz), 7,67 (1H, d, J = 9,3 Hz), 7,41-7,36 (1H, m), 7,14-7,04 (3H, m), 5,72 (2H, s), 4,58 (2H, t, J = 5,4 Hz), 4,54 (2H, t, J = 5,4 Hz), 3,24 (3H, s), 2,26 (3H, s).

Passo 3 Síntese de 4-(3-cloro-4-3-fluorobenziloxi)fenilamino)-6-(1-2-etilaminoetoxiimino)-2-butin-1-il)quinazolina (VIII-35)

4-(3-Cloro-4-(3-fluorobenziloxi)fenilamino)-6-(1-(2-sulfoniloxiethoxiimino)-2-butin-1-il)quinazolina (VIII-34, 100 mg) foi dissolvida em 3 mL de N,N-dimetilformamida e foi adicionado 160 µg de solução de aquosa etilamina a 70%, seguido de agitação a 60 °C durante 14 horas. Foi adicionada água à

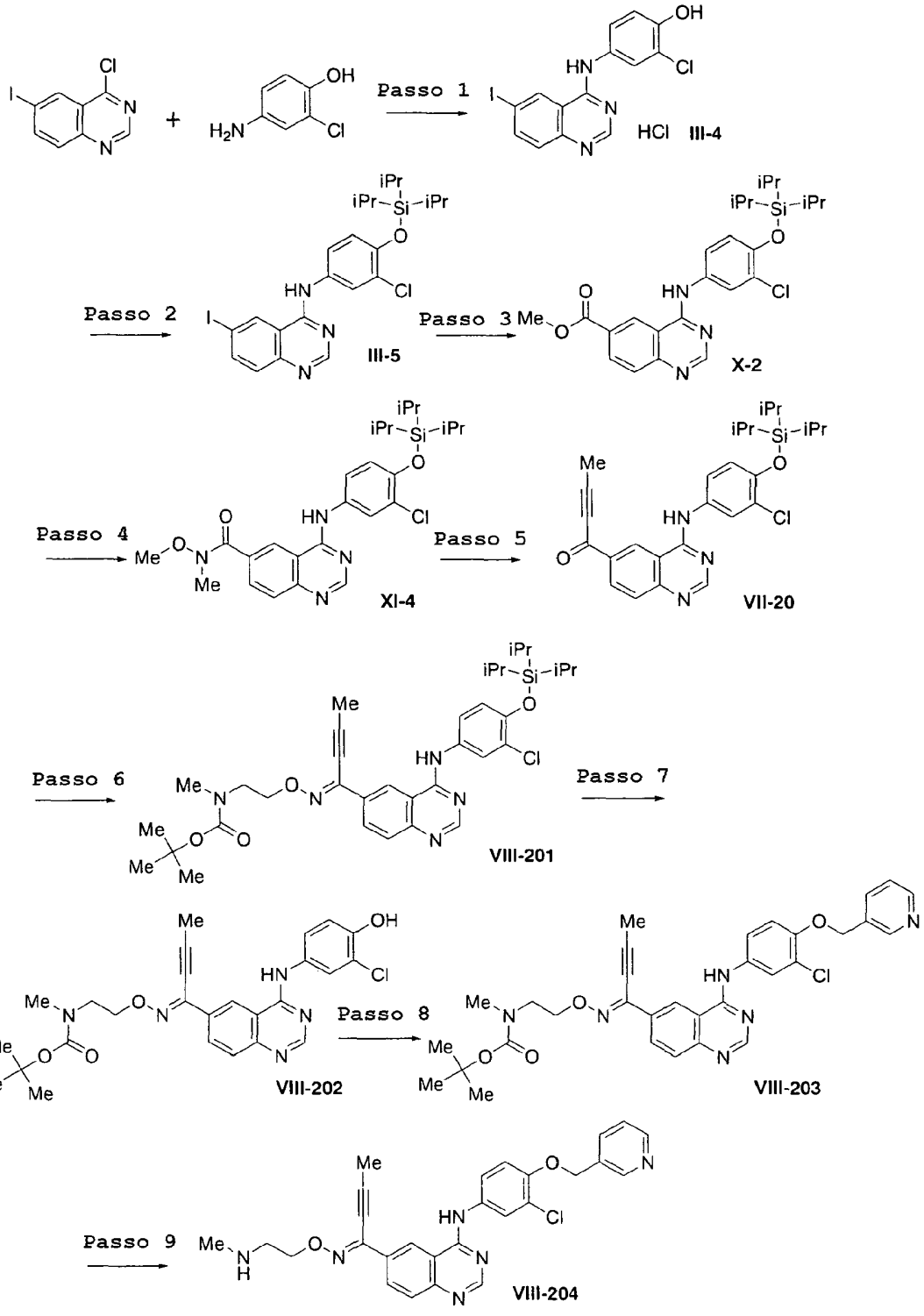
mistura reaccional, seguida de extracção com acetato de etilo. A camada orgânica foi seca sobre sulfato de magnésio e o resíduo concentrado do filtrado foi purificado por cromatografia (eluindo com acetato de etilo) utilizando uma coluna amino para obter 4-(3-cloro-4-3-fluorobenziloxi)fenilamino)-6-(1-(2-etilaminoetoxiimino)-2-butin-1-il)quinazolina (VIII-35, 53 mg) como um sólido incolor.

RMN de ^{1}H (d_6-DMSO, δ): 10,08 (1H, s), 8,74 (1H, s), 8,59 (1H, s), 8,21 (1H, d, J = 8,4 Hz), 7,96 (1H, s), 7,80 (1H, d, J = 8,8 Hz), 7,69 (1H, d, J = 8,0 Hz), 7,51- 7,45 (1H, m), 7,35-7,27 7 (3H, m), 7,21-7,16 (1H, m), 5,27 (2H, s), 4,31 (2H, t. J = 5,6 Hz), 2,89 (2H, t, J = 6,0 Hz), 2,61 (2H, q, J = 7,2 Hz), 2,26 (3H, s), 1,02 (3H, t, J = 7,6 Hz).

Na aminação do terceiro passo pode ser utilizada uma amina que está comercialmente disponível ou uma amina que pode ser sintetizada de acordo com o método descrito em J. Syn. Org. Chem., Jpn., 2001, 59:779-789, Tetrahedron Lett., 1995, 36:6373-6374, Synlett, 1999:1301-1303, Tetrahedron, 2002, 58:6267-6276 ou um seu sal.

Exemplo 10

Fórmula química 80



Passo 1 Síntese de 4-(3-Cloro-4-hidroxifenilamino)-6-Iodoquinazolina (III-4)

De acordo com o mesmo modo que o do primeiro passo do Exemplo 1 e utilizando 20,3 g de 4-cloro-6-iodoquinazolina e 10 g de 3-cloro-4-hidroxianilina foi obtido cloridrato de 4-(3-cloro-4-hidroxifenilamino)-6-iodoquinazolina (III-4, 26,6 g) como um sólido amarelo.

RMN de ^{1}H (d_6-DMSO, δ): 11,4 (1H, s), 10,5 (1H, s), 9,21 (1H, s), 8,93 (1H, s), 8,35 (1H, d, J = 8,4 Hz), 7,79 (1H, s), 7,69 (1H, d, J = 9,0 Hz), 7,48 (1H, d, J = 9,0 Hz), 7,10 (1H, d, J = 8,4 Hz).

Passo 2 Síntese de 4-(3-cloro-4-triisopropilsililoxi-fenilamino)-6-iodoquinazolina (III-5)

Cloridrato de 4-(3-cloro-4-3-fluorobenziloxi)fenilamino)-6-iodoquinazolina (III-4, 20 g), 13,3 g de cloreto de triisopropilsilano e 12,6 g de imidazole foram dissolvidos em 200 mL de N,N-dimetilformamida, seguido de agitação à temperatura ambiente durante 4 horas. Depois de a reacção estar completa, foram adicionados 200 mL de solução aquosa saturada de bicarbonato de sódio e 200 mL de acetato de etilo para separar as camadas. A camada aquosa foi reextraída duas vezes com 200 mL de acetato de etilo, e todas as camadas orgânicas foram combinadas, lavadas com água e solução aquosa saturada de cloreto de sódio por esta ordem, e secas sobre sulfato de magnésio anidro. O filtrado foi concentrado e o resíduo foi lavado com um hexano-acetato de etilo (2:1) para obter

4-(3-cloro-4-triisopropilsililoxifenilamino)-6-iodoquinazolina (III-5, 25,3 g) como um sólido incolor.

RMN de ^{1}H (d_6-DMSO, δ): 9,8 (1H, s), 8,96 (1H, s), 8,62 (1H, s), 8,12 (1H, d, J = 8,7 Hz), 8,02 (1H, d, J = 2,7 Hz), 7,70 (1H, dd, J = 8,7 Hz, J = 2,7 Hz), 7,56 (1H, d, J = 8,7 Hz), 7,04 (1H, d, J = 8,7 Hz), 1,25-1,40 (3H, m), 1,11 (18H, d, J = 7,2 Hz).

Passo 3 Síntese de éster metílico do ácido 4-(3-cloro-4-triisopropilsililoxifenilamino)-quinazolina-6-carboxílico (X-2)

A partir de 4-(3-cloro-4-triisopropilsililoxifenilamino)-6-iodoquinazolina (III-5, 21,8 g), o éster metílico do ácido 4-(3-cloro-4-triisopropilsililoxifenilamino)-quinazolina-6-carboxílico (X-2, 20,4 g) foi obtido como um sólido amarelo de acordo com o mesmo modo que o do primeiro passo do Exemplo de Referência 1.

RMN de ^{1}H (d_6-DMSO, δ): 10,2 (1H, s), 9,26 (1H, s), 8,66 (1H, s), 8,30 (1H, d, J = 8,7 Hz), 8,01 (1H, d, J = 2,4 Hz), 7,84 (1H, d, J = 8,7 Hz), 7,71 (1H, dd, J = 9 Hz, J = 2,1 Hz), 7,04 (1H, d, J = 8,7 Hz), 3,96 (3H, s), 1,29-1,41 (3H, m), 1,11 (18H, d, J = 7,2 Hz).

Passo 4 Síntese de metoximetilamida do ácido 4-(3-cloro-4-triisopropilsililoxifenilamino)-quinazolina-6-carboxílico (XI-4)

A partir de éster metílico do ácido 4-(3-cloro-4-triisopropilsililoxifenilamino)-quinazolina-6-carboxílico (X-2, 10 g), a metoximetilamida do ácido 4-(3-cloro-4-

triisopropilsililoxifenilamino)-quinazolina-6-carboxílico (XI-4, 4,1 g) foi obtida como um sólido incolor de acordo com o mesmo modo que o do segundo passo do Exemplo de Referência 1.

RMN de ^{1}H (d_6-DMSO, δ): 10,0 (1H, s), 8,80 (1H, s), 8,65 (1H, s), 7,97-8,08 (2H, m), 7,81 (1H, d, J = 8,7 Hz), 7,70-7,75 (1H, m), 7,04 (1H, d, J = 9,0 Hz), 3,58 (3H, s), 3,35 (3H, s), 1,29-1,41 (3H, m), 1,11 (18H, d, J = 7,5 Hz).

Passo 5 Síntese de 4-(3-cloro-4-triisopropilsililoxifenilamino)-6-(1-oxo-2-butin-1-il)quinazolina (VII-20)

A partir de metoximetilamida do ácido 4-(3-cloro-4-triisopropilsililoxifenilamino)-quinazolina-6-carboxílico (XI-4, 4,1 g), a 4-(3-cloro-4-triisopropilsililoxifenilamino)-6-(1-oxo-2-butin-1-il)quinazolina (VII-20, 1,3 g) foi obtida como um óleo amarelo de acordo com o mesmo modo que o do terceiro passo do Exemplo de Referência 1.

RMN de ^{1}H (d_6-DMSO, δ): 10,3 (1H, s), 9,24 (1H, s), 8,67 (1H, s), 8,45 (1H, d, J = 8,7 Hz), 7,99 (1H, s), 7,88(1H, s, J = 8,7 Hz), 7,68 (1H, d, J = 9,0 Hz), 7,06 (1H, d, J = 9,0 Hz), 2,28 (3H, s), 1,29-1,41 (3H, m), 1,11 (18H, d, J = 6,9 Hz).

Passo 6 Síntese de 4-(3-cloro-4-triisopropilsililoxifenilamino)-6-(1-(2-(N-(terc-butoxicarbonil)-N-metilaminoetoxiimino)-2-butin-1-il)quinazolina (VIII-201)

A partir de 4-(3-cloro-4-triisopropilsililoxifenilamino)-6-(1-oxo-2-butin-1-il)quinazolina (VII-20, 1,3 g), a 4-(3-cloro-4-triisopropilsililoxifenilamino)-6-(1-(2-(N-(terc-butoxicarbonil)-N-metilaminoetoxiimino)-2-butin-1-il)quinazolina (VIII-201, 1,1 g) foi obtida como um sólido amarelo de acordo com o mesmo modo que o do segundo passo do Exemplo 2. ESI-MS (M/Z): (M+) = 666,71, (M+H) = 667,73

Passo 7 Síntese de 4-(3-cloro-4-hidroxifenilamino)-6-(1-(2-(N-(terc-butoxicarbonil)-N-metilaminoetoxiimino)-2-butin-1-il)quinazolina (VIII-202)

4-(3-Cloro-4-triisopropilsililoxifenilamino)-6-(1-(2-(N-(terc-butoxicarbonil)-N-metilaminoetoxiimino)-2-butin-1-il)quinazolina (VIII-201, 1,1 g) foi dissolvida em 20 mL de tetra-hidrofurano e foram adicionados 6,7 mL de solução de fluoreto de tetrabutilamónio a 1 mol/L em tetra-hidrofurano, seguido de agitação à temperatura ambiente durante 30 minutos. Depois de a reacção estar completa, foram adicionados 10 mL de água e 10 mL de acetato de etilo para separar as camadas. A camada aquosa foi reextraída duas vezes com 10 mL de acetato de etilo, e todas as camadas orgânicas foram combinadas, lavadas com água e solução aquosa saturada de cloreto de sódio, e secas sobre sulfato de magnésio anidro. O filtrado foi concentrado e o resíduo foi lavado com hexano-acetato de etilo (1:1) para obter 4-(3-cloro-4-hidroxifenilamino)-6-(1-(2-(N-(terc-

butoxicarbonil)-N-metilaminoetoxiimino)-2-butin-1-il)quinazolina (VIII-202, 0,7 g) como um sólido amarelo.

RMN de ^{1}H (d_6-DMSO, δ): 9,96 (1H, s), 8,73 (1H, s), 8,55 (1H, s), 8,21 (1H, d, J = 8,7 Hz), 7,75-7,86 (2H, m), 7,50 (1H, d, J = 7,8 Hz), 7,00 (1H, d, J = 8,7 Hz), 4,36 (2H, sl), 3,56 (2H, sl), 2,86 (3H, sl), 2,25 (3H, sl), 1,36 (9H, s).

Passo 8 Síntese de 4-(3-cloro-4-(piridin-3-ilmetoxi)fenilamino)-6-(1-(2-(N-(terc-butoxicarbonil)-N-metilaminoetoxiimino)-2-butin-1-il)quinazolina (VIII-203)

4-(3-Cloro-4-hidroxifenilamino)-6-(1-(2-(N-(terc-butoxicarbonil)-N-metilaminoetoxiimino)-2-butin-1-il)quinazolina (VIII-202, 70 mg), 87 mg de bromidrato de 3-bromometilpiridina e 223 mg de carbonato de césio foram dissolvidos em 1,1 mL de N,N-dimetilformamida-água (10,1), seguido de agitação à temperatura ambiente durante 3 horas. Depois de a reacção estar completa, foram adicionados 5 mL de água e 5 mL de acetato de etilo para separar as camadas. A camada aquosa foi reextraída duas vezes com 5 mL de acetato de etilo, e todas as camadas orgânicas foram combinadas, lavadas com água e solução aquosa saturada de cloreto de sódio por esta ordem, e secas sobre sulfato de magnésio anidro. O filtrado foi concentrado e o resíduo foi purificado por cromatografia em coluna sobre sílica gel (eluindo com hexano: acetato de etilo = 1:1) para obter 4-(3-cloro-4-(piridin-3-ilmetoxi)fenilamino)-6-(1-(2-(N-(terc-butoxicarbonil)-N-metilaminoetoxiimino)-2-butin-1-il)quinazolina (VIII-203, 70 mg) como um óleo amarelo.

RMN de ^1H (d_6-DMSO, δ): 10,0 (1H, sl), 8,74 (1H, sl), 8,72 (1H, sl), 8,60 (1H, s), 8,57 (1H, d, J = 4,4 Hz), 8,23 (1H, d, J = 8,8 Hz), 7,97 (1H, sl), 7,91 (1H, d, J = 8,0 Hz), 7,80 (1H, d, J = 8,8 Hz), 7,72 (1H, d, J = 8,8 Hz), 7,46 (1H, dd, J = 7,6 Hz, J = 4,4 Hz), 7,33 (1H, d, J = 8,8 Hz), 5,29 (2H, s), 4,37 (2H, sl), 3,56 (2H, sl), 2,86 (3H, sl), 2,25 (3H, sl), 1,36 (9H, s).

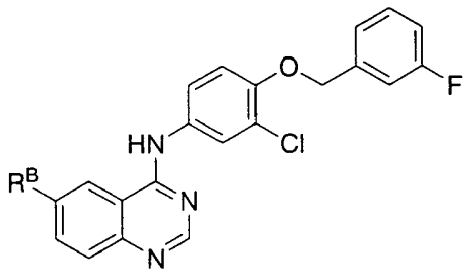
Passo 9 Síntese de 4-(3-cloro-4-(piridin-3-ilmetoxi)fenilamino)-6-(1-(2-N-metilaminoetoxiimino)-2-butin-1-il)quinazolina (VIII-204)

Partindo de 4-(3-cloro-4-(piridin-3-ilmetoxi)fenilamino)-6-(1-(2-(N-(terc-butoxicarbonil)-N-metilaminoetoxiimino)-2-butin-1-il)quinazolina (VIII-203, 70 mg), e de acordo com o mesmo modo que o do segundo passo do Exemplo 2, foi realizada a reacção e foi realizada a purificação por recristalização a partir de hexano-acetato de etilo para obter 4-(3-cloro-4-(piridin-3-ilmetoxi)fenilamino)-6-(1-(2-N-metilaminoetoxiimino)-2-butin-1-il)quinazolina (VIII-204, 7 mg) como um sólido amarelo.

10,3 (1H, s), 8,84 (1H, s), 8,72 (1H, s), 8,42-8,65 (2H, m), 8,26 (1H, d, J = 7,6 Hz), 7,98 (1H, s), 7,91 (1H, s l), 7,81 (1H, s l), 7,71 (1H, s l), 7,47 (1H, s l), 7,34 (1H, d, J = 8,0 Hz), 5,30 (2H, s), 4,53 (2H, s l), 3,38 (2H, s l), 2,68 (3H, s), 2,26 (3H, s).

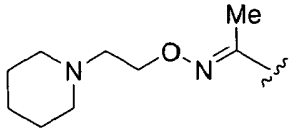
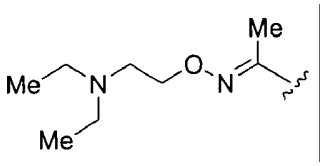
De acordo com o mesmo modo que o dos Exemplos 7 a 10 foi sintetizado o composto seguinte.

Fórmula química 81

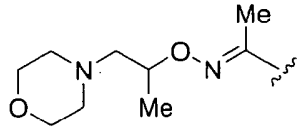
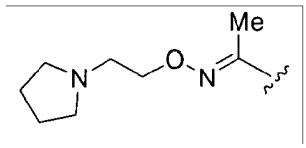
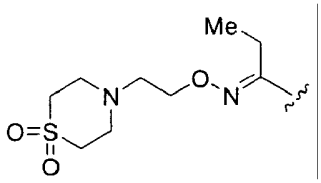


(VIII)

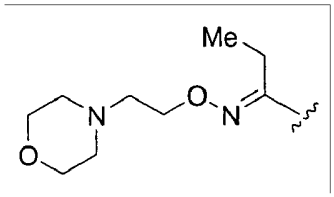
Quadro 15

Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-2		9,92(1H, s), 8,65(1H, s l), 8,62(1H, s), 8,22(1H, d, J = 6,6 Hz), 7,96(1H, d, J = 2,1 Hz), 7,76(1H, d, J = 6,6 Hz), 7,70(1H, dd, J = 6,6 Hz, J = 1,8 Hz), 7,53-7,45(1H, m), 7,35-7,28(3H, m), 7,18(1H, t, J = 5,7 Hz), 5,27(2H, s), 4,30(2H, t, J = 4,5 Hz), 2,64(2H, t, J = 4,5 Hz), 2,43(4H, s l), 2,35(3H, s), 1,53-1,47(4H, m), 1,40-1,36(2H, m).
VIII-3		9,92(1H, s), 8,62(1H, s l), 8,58(1H, s), 8,23(1H, d, J = 6,6 Hz), 7,96(1H, d, J = 1,8 Hz), 7,76(1H, d, J = 6,6 Hz), 7,70(1H, d, J = 6,9 Hz), 7,50-7,45(1H, m), 7,35-7,28(3H, m), 7,18(1H, t, J = 6,9 Hz), 5,27(2H, s), 4,26(2H, t, J = 4,5 Hz), 2,77(2H, t, J = 4,5 Hz), 2,55(4H, q, J = 5,4 Hz), 2,36(3H, s), 0,96(2H, t, J = 5,4 Hz)

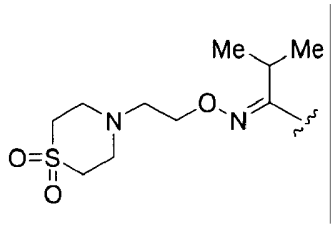
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Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-4		(sal de mono-HCl) 11,4(1H, s l), 10,82(1H, s l), 9,07(1H, s), 8,82(1H, s), 8,40(1H, d, J = 10,2 Hz), 7,94(1H, d, J = 2,7 Hz), 7,88(1H, d, J = 9,0 Hz), 7,70(1H, dd, J = 8,7 Hz, 2,7 Hz), 7,45-7,52(1H, m), 7,31-7,36(3H, m), 7,17-7,23(1H, m), 5,30(2H, s), 4,94(1H, m), 3,85(4H, m), 3,36-3,60(6H, m), 2,44(3H, s), 1,38(3H, d, J = 6,3 Hz)
VIII-5		9,93(1H, s), 8,62(1H, s l), 8,58(1H, s), 8,22(1H, d, J = 6,6 Hz), 7,96(1H, d, J = 1,8 Hz), 7,76(1H, d, J = 6,6 Hz), 7,70(1H, dd, J = 6,6 Hz, J = 1,8 Hz), 7,50-7,45(1H, m), 7,35-7,28(3H, m), 7,19(1H, t, J = 6,6 Hz), 5,27(2H, s), 4,31(2H, t, J = 4,5 Hz), 2,78(2H, t, J = 4,5 Hz), 2,50(4H, l), 2,36(3H, s), 1,69(4H, l)
VIII-6		9,95(1H, s), 8,62(1H, s l), 8,58(1H, s), 8,21(1H, d, J = 6,9 Hz), 7,94(1H, d, J = 1,5 Hz), 7,77(1H, d, J = 6,6 Hz), 7,69(1H, d, J = 6,9 Hz), 7,51-7,45(1H, m), 7,35-7,28(3H, m), 7,19(1H, t, J = 6,3 Hz), 5,28(2H, s), 4,32(2H, t, J = 4,2 Hz), 3,09(4H, d l, J = 4,5 Hz), 3,05(4H, d l, J = 4,5 Hz), 2,97-2,89(4H, m), 1,13(3H, t, J = 5,4 Hz)

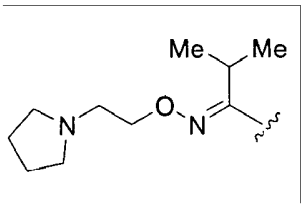
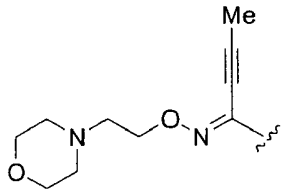
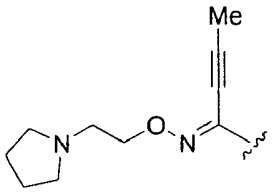
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Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-7		9,95(1H, s), 8,61(1H, s l), 8,58(1H, s), 8,20(1H, d, J = 6,6 Hz), 7,94(1H, s l), 7,77(1H, d, J = 6,6 Hz), 7,69(1H, d, J = 6,9 Hz), 7,51-7,45(1H, m), 7,35-7,28(3H, m), 7,19(1H, t, J = 6,0 Hz), 5,27(2H, s), 4,32(2H, t, J = 4,2 Hz), 3,59(4H, t, J = 3,3 Hz), 2,91(2H, q, J = 5,4 Hz), 2,68(2H, t, J = 4,2 Hz), 1,13(3H, t, J = 5,4 Hz)

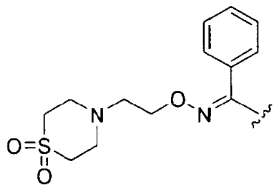
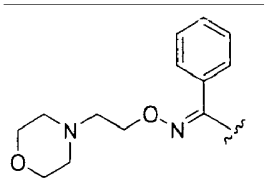
Quadro 16

Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-8		(mistura E/Z) 8,61 (0,5H, s), 8,58 (0,5H, s), 8,48 (0,5H, s), 8,25 (0,5H, s), 7,99 (0,5H, d, J = 2,4 Hz), 7,97 (0,5H, d, J = 2,4 Hz), 7,90 (0,5H, d, J = 7,9 Hz), 7,65-7,73 (2,5H, m), 7,50-7,55 (0,5H, m), 7,26-7,34 (3,5H, m), 7,16 (1H, d,t J = 7,9,2,4 Hz), 5,26 (2H, s), 4,29 (1H, t, J = 7,0 Hz), 4,15 (1H, t, J = 7,0 Hz), 3,50-3,55 (1H, m) , 3,28-3,35 (2H, m), 3,20-3,28 (2H, m), 3,10-3,20 (2H, m), 2,99-3,07 (2H, m), 2,90-2,96 (1H, m), 2,87-2,95 (1H, m), 1,21 (3H, d, J = 7,0 Hz), 1,16 (3H, d, J = 7,0 Hz)

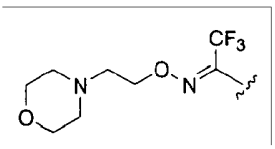
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Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-9		(mistura E/Z) 8,58 (0,5H, s), 8,56 (0,5H, s), 8,44 (0,5H, s), 8,36 (0,5H, s), 7,99 (0,5H, d, J = 2,4 Hz), 7,97 (0,5H, d, J = 2,4 Hz), 7,90 (0,5H, d, J = 7,9 Hz), 7,65-7,73 (2,5H, m), 7,50-7,55 (0,5H, m), 7,26-7,34 (3,5H, m), 7,16 (1H, d,t J = 7,9,2,4 Hz), 5,24 (2H, s), 4,21 (1H, t, J = 7,0 Hz), 4,05 (1H, t, J = 7,0 Hz), 2,73 (1H, t, J = 7,2 Hz), 2,57 (1H, t, J = 7,2 Hz), 2,45-2,55 (2H, m), 2,30-2,35 (2H, m), 1,64-1,70 (2H, m), 1,50-1,58 (2H, m), 1,21 (3H, d, J = 7,0 Hz), 1,16 (3H, d, J = 7,0 Hz)
VIII-10		(mistura E/Z) 10,09(1H, s, maior), 10,00(1H, s, menor), 8,74(1H, s, maior), 8,59(1H, s), 8,22(1H, d, J = 9 Hz, maior), 7,94-8,02(1H, m), 7,64-7,82(2H, m), 7,44-7,52(1H, m), 7,16-7,36(4H, m), 5,27(2H, s), 4,32-4,43(2H, m), 3,56-3,62(4H, m), 2,66-2,74(2H, m), 2,34(3H, s, menor), 2,25(3H, s, maior)
VIII-11		10,08(1H, s), 8,74(1H, s), 8,58(1H, s), 8,22(1H, d, J = 8,4 Hz), 7,96(1H, s l), 7,80(1H, d, J = 8,4 Hz), 7,68(1H, d, J = 9,6 Hz), 7,43- 7,52(1H, m), 7,14- 7,36(4H, m), 5,27(2H, s), 4,37(2H, t, J = 6,0 Hz), 2,80(2H, t, J = 6,0 Hz), 2,25(3H, s), 1,69(4H, s l), 1,24(4H, s l)

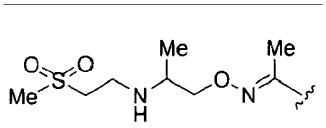
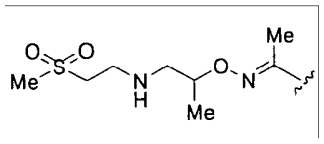
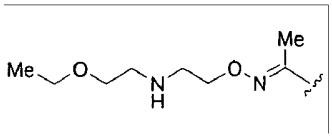
(continuação)

Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-12		(mistura E/Z) 9,95(1H, s, maior), 9,80(1H, s, menor), 8,65(1H, s, menor), 8,58(1H, s, maior), 8,54(1H, s, maior), 8,44(1H, s, menor), 7,99(1H, d, J = 1,5 Hz, menor), 7,91(1H, d, J = 1,8 Hz, maior), 7,15-7,92(14H, m), 5,26(2H, s), 5,25(2H, s), 4,32(2H, d, J = 3,9 Hz, maior), 4,27(2H, t, J = 4,2 Hz, menor), 2,82-3,06(10H, m)
VIII-13		(mistura E/Z) 9,96(1H, s, maior), 9,82(1H, s, menor), 8,64(1H, s, menor), 8,57(1H, s, maior), 8,53(1H, s l, maior), 8,44(1H, s l, menor), 7,99(1H, d, J = 2,7 Hz, menor), 7,90(1H, d, J = 2,4 Hz, maior), 7,14- 7,88(13H, m), 5,26(2H, s, maior), 5,24(2H, s, menor), 4,32(2H, t, J = 5,7 Hz, maior), 4,27(2H, t, J = 5,4 Hz, menor), 3,53-3,58(4H, m, maior), 3,44-3,50(4H, m, menor), 2,56-2,70(2H, m), 2,32-2,46(4H, m)

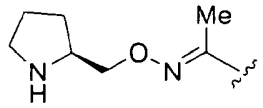
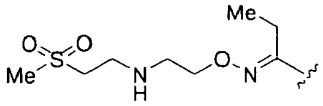
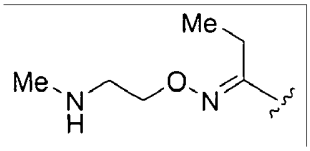
Quadro 17

Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-14		9,99(1H, s), 8,65(s, 1H), 8,61(1H, s), 7,98(1H, s l), 7,90(1H, d, J = 6,9 Hz), 7,87(1H, d, J = 6,9 Hz), 7,70(1H, d, J = 6,3 Hz), 7,40-7,51(1H, m), 7,27-7,35(3H, m), 7,15-7,21(1H, m), 5,27(2H, s), 4,38(2H, t, J = 3,9 Hz), 3,47-3,51(4H, m), 2,57-2,65(2H, m), 2,33-2,40(4H, m)

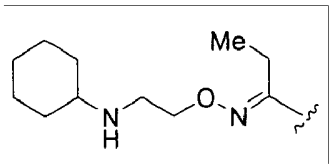
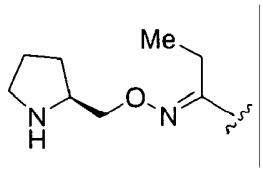
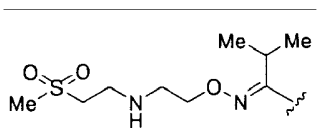
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Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-15		9,94(1H, s), 8,63(1H, s), 8,58(1H, s), 8,23(1H, dd, J = 8,7 Hz, 1,2 Hz), 7,96(1H, d, J = 2,4 Hz), 7,76(1H, d, J = 9,0 Hz), 7,70(1H, dd, J = 8,4 Hz, 2,4 Hz), 7,44-7,52(1H, m), 7,28-7,35(3H, m), 7,16-7,22(1H, m), 5,27(2H, s), 4,07-4,10(2H, m), 3,23(2H, t, J = 6,9 Hz), 3,01-3,04(6H, m), 2,38(3H, s), 1,05(3H, d, J = 6,3 Hz)
VIII-16		9,94(1H, s), 8,62(1H, s), 8,58(1H, s), 8,25(1H, dd, J = 9,0 Hz, 1,5 Hz), 7,95(1H, d, J = 2,7 Hz), 7,76(1H, d, J = 8,7 Hz), 7,69(1H, dd, J = 8,7 Hz, 2,4 Hz), 7,44-7,52(1H, m), 7,28-7,35(3H, m), 7,16-7,22(1H, m), 5,27(2H, s), 4,39-4,45(1H, m), 3,25(2H, t, J = 6,9 Hz), 2,95-3,01(5H, m), 2,73-2,92(2H, m), 2,36(3H, s), 1,30(3H, d, J = 6,3 Hz)
VIII-17		(sal de di-HCl) 11,09(1H, s l), 9,00(1H, s), 8,90(2H, s l), 8,75(1H, s), 8,34(1H, d, J = 9,3 Hz), 7,96(1H, d, J = 2,7 Hz), 7,85(1H, d, J = 8,7 Hz), 7,72(1H, dd, J = 9,0 Hz, 2,7 Hz), 7,45-7,52(1H, m), 7,31-7,35(3H, m), 7,17-7,22(1H, m), 5,29(2H, s), 4,49(2H, t, J = 5,4 Hz), 3,67(2H, t, J = 5,4 Hz), 3,49(2H, q, J = 6,9 Hz), 3,21-3,23(4H, m), 2,45(3H, s), 1,13(3H, t, J = 6,9 Hz)

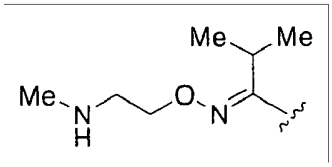
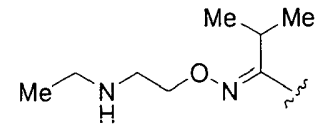
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Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-18		9,93(1H, s), 8,62(1H, s l), 8,58(1H, s), 8,22(1H, d, J = 6,9 Hz), 7,95(1H, s l), 7,76(1H, d, J = 6,0 Hz), 7,70(1H, d, J = 6,3 Hz), 7,50-7,45(1H, m), 7,35-7,28(3H, m), 7,18(1H, t, J = 5,4 Hz), 5,27(2H, s), 4,11-4,03(2H, m), 2,87-2,67(2H, m), 2,37(3H, s), 1,85-1,76(1H, m), 1,73-1,59(2H, m), 1,48-1,39(1H, m)
VIII-19		(sal de bis-trifluoroacetato) 11,40(1H, s), 9,10(2H, s), 8,89(1H, s), 8,81(1H, s), 8,42(1H, d, J = 6,0 Hz), 7,90-7,87(2H, m), 7,62(1H, d, J = 6,6 Hz), 7,51-7,46(1H, m), 7,38-7,31(3H, m), 7,20(1H, t, J = 6,3 Hz), 5,32(2H, s), 4,48(2H, s l), 3,61-3,46(6H, m), 3,13(3H, s), 2,97(2H, q, J = 5,7 Hz), 1,14(3H, t, J = 5,7 Hz).
VIII-20		(sal de bis-trifluoroacetato) 11,07(1H, s), 8,82(1H, s), 8,78(3H, s l), 8,37(1H, d, J = 6,6 Hz), 7,89-7,86(2H, m), 7,64(1H, d, J = 6,6 Hz), 7,51-7,46(1H, m), 7,36-7,32(3H, m), 7,20(1H, t, J = 6,3 Hz), 5,31(2H, s), 4,45(2H, s l), 2,97(2H, q, J = 5,4 Hz), 2,67(3H, s l), 1,13(3H, t, J = 5,4 Hz).

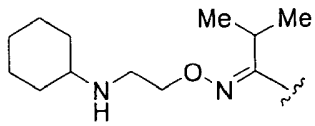
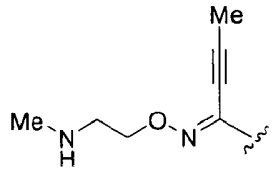
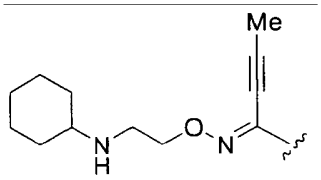
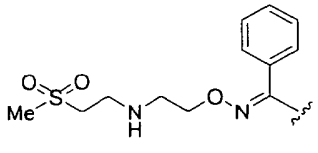
Quadro 18

Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-21		(sal de bis-trifluoroacetato) 11,03(1H, s), 8,81(1H, s), 8,78(1H, s), 8,71(2H, s), 8,37(1H, d, J = 6,6 Hz), 7,88-7,86(2H, m), 7,64(1H, d, J = 6,6 Hz), 7,51-7,46(1H, m), 7,36-7,31(3H, m), 7,20(1H, t, J = 6,3 Hz), 5,31(2H, s), 4,46(2H, s l), 3,39(2H, s l), 3,10(1H, s l), 2,97(2H, q, J = 6,3 Hz), 2,06(2H, d l, J = 8,4 Hz), 1,78(2H, d l, J = 8,4 Hz), 1,37-1,04(9H, m).
VIII-22		9,95(1H, s), 8,61(1H, s l), 8,58(1H, s), 8,19(1H, d, J = 6,3 Hz), 7,94(1H, s l), 7,77(1H, d, J = 6,6 Hz), 7,69(1H, d, J = 6,6 Hz), 7,50-7,45(1H, m), 7,35-7,28(3H, m), 7,19(1H, t, J = 6,0 Hz), 5,27(2H, s), 4,14-4,07(2H, m), 3,43(1H, l), 2,95-2,82(4H, m), 1,86-1,80(1H, m), 1,69(2H, m), 1,46(1H, m), 1,14(3H, t, J = 5,4 Hz)
VIII-23		(mistura E/Z) 8,60 (0,5H, s), 8,58 (0,5H, s), 8,47 (0,5H, s), 8,39 (0,5H, s), 7,96 (0,5H, d, J = 2,4 Hz), 7,93 (0,5H, d, J = 2,4 Hz), 7,88 (0,5H, d, J = 7,9 Hz), 7,65-7,73 (2,5H, m), 7,50- 7,55 (0,5H, m), 7,26-7,34 (3,5H, m), 7,16 (1H, d,t J = 7,9,2,4 Hz), 5,26 (2H, s), 4,19 (1H, t, J = 7,0 Hz), 4,03 (1H, t, J = 7,0 Hz), 3,50-3,55 (1H, m) , 3,22-3,30 (1H, m), 3,16-3,23 (1H, m), 2,96-3,03 (1H, m), 3,04 (1,5H, s), 2,90-2,95 (2H, m), 2,93 (1,5H, s), 2,70-2,80 (1H, m), 1,21 (3H, d, J = 7,0 Hz), 1,16 (3H, d, J = 7,0 Hz)

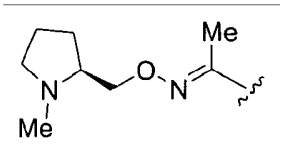
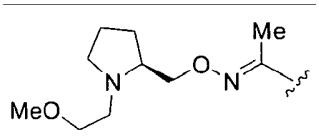
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Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-24		(mistura E/Z) 8,61 (0,5H, s), 8,59 (0,5H, s), 8,47 (0,5H, s), 8,41 (0,5H, s), 7,99 (0,5H, d, J = 2,4 Hz), 7,97 (0,5H. d, J = 2,4 Hz), 7,90 (0,5H, d, J = 7,9 Hz), 7,65-7,73(2,5H, m), 7,50-7,55 (0,5H, m), 7,26-7,34 (3,5H, m), 7,16 (1H, d,t J = 7,9,2,4 Hz), 5,26 (2H, s), 4,29 (1H, t, J = 7,0 Hz), 4,13 (1H, t, J = 7,0 Hz), 3,50-3,55 (1H, m) , 3,14-3,30 (1H, m) , 2,96-3,04 (1H, m) , 2,54 (1,5H, s) , 2,49 (1,5H, s), 1,21 (3H, d, J = 7,0 Hz), 1,16 (3H, d, J = 7,0 Hz), 1,00 (3H, t, J = 7,2 Hz)
VIII-25		(mistura E/Z) 8,61 (0,5H, s), 8,58 (0,5H, s), 8,48 (0,5H, s), 8,31 (0,5H, s), 7,99 (0,5H, d, J = 2,4 Hz), 7,97 (0,5H, d, J = 2,4 Hz), 7,90 (0,5H, d, J = 7,9 Hz), 7,65-7,73 (2,5H, m), 7,50-7,55 (0,5H, m), 7,26-7,34 (3,5H, m), 7,16 (1H, d,t J = 7,9,2,4 Hz), 5,26 (2H, s), 4,29 (1H, t, J = 7,0 Hz), 4,15 (1H, t, J = 7,0 Hz), 3,50-3,55 (1H, m) , 3,24-3,30 (1H, m) , 3,10-3,14 (1H, m) , 2,99 (1H, q, J = 7,2 Hz), 2,89 (1H, q, J = 7,2 Hz), 1,21 (3H, d, J = 7,0 Hz), 1,16 (3H, d, J = 7,0 Hz), 1,00 (3H, t, J = 7,2 Hz)

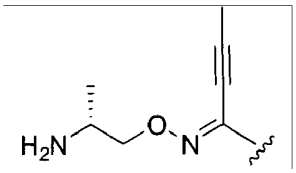
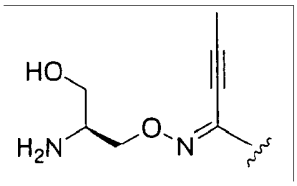
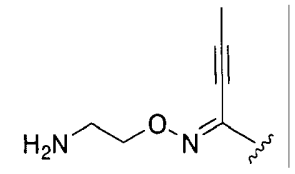
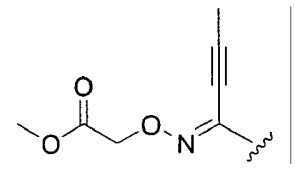
Quadro 19

Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-26		(mistura E/Z) 8,61 (0,5H, s), 8,58 (0,5H, s), 8,48 (0,5H, s), 8,31 (0,5H, s), 7,99 (0,5H, d, J = 2,4 Hz), 7,94 (0,5H, d, J = 2,4 Hz), 7,90 (0,5H, d, J = 7,9 Hz), 7,65-7,73 (2,5H, m), 7,50-7,55 (0,5H, m), 7,26-7,34 (3,5H, m), 7,16 (1H, d,t J = 7,9,2,4 Hz), 5,26 (2H, s), 4,29 (1H, t, J = 7,0 Hz), 4,11 (1H, t, J = 7,0 Hz), 3,50-3,55 (1H, m) , 3,14-3,17 (1H, m) , 3,00-3,04 (1H, m) , 2,00-2,10 (2H, m), 1,70-1,85 (2H, m), 1,00-1,30 (6H, m), 1,23 (3H, d, J = 7,0 Hz), 1,16 (3H, d, J = 7,0 Hz)
VIII-27		10,10(1H, s), 8,76(1H, s), 8,60(1H, s), 8,25(1H, d, J = 8,7 Hz), 7,96(1H, s l), 7,82(1H, d, J = 9,0 Hz), 7,69(1H, d, J = 9,0 Hz), 7,43-7,52(1H, m), 7,14-7,36(4H, m), 5,28(2H, s), 4,43(2H, s l), 2,98(2H, s l), 2,54(3H, s), 2,27(3H, s l), 1,60(1H, s)
VIII-28		10,10(1H, s), 8,77(1H, s), 8,60(1H, s), 8,25(1H, d, J = 8,7 Hz), 7,95(1H, s l), 7,82(1H, d, J = 9,6 Hz), 7,69(1H, d, J = 9,3 Hz), 7,43-7,52(1H, m), 7,14-7,36(4H, m), 5,28(2H, s), 4,45(2H, s l), 2,91(2H, s l), 2,27(3H, s), 2,00(2H, s l), 1,73(2H, s l), 1,60(1H, s l), 1,23(7H, s l)
VIII-29		(mistura E/Z) 9,94(1H, s, maior), 9,78(1H, s, menor), 8,62(1H, s, menor), 8,56(1H, s, maior), 8,51(1H, s l, maior), 8,42(1H, s l, menor), 7,12-7,53(14H, m), 5,24(2H, s,), 4,15-4,28(2H, m), 3,13-3,25(2H, m), 2,80-3,00(7H, m)

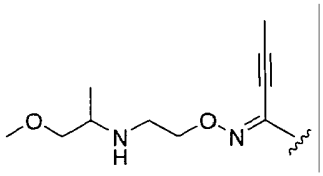
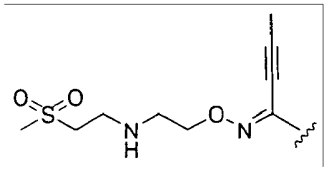
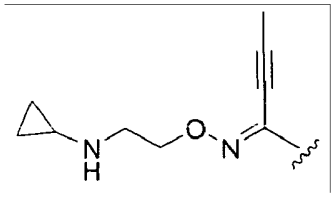
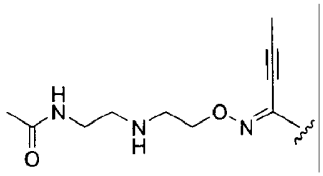
(continuação)

Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-30		9,93(1H, s), 8,62(1H, s l), 8,58(1H, s), 8,22(1H, d, J = 6,3 Hz), 7,96(1H, d, J = 1,2 Hz), 7,76(1H, d, J = 6,6 Hz), 7,70(1H, d, J = 6,6 Hz), 7,50-7,45(1H, m), 7,35-7,28(3H, m), 7,19(1H, t, J = 6,6 Hz), 5,27(2H, s), 4,23(1H, dd, J = 8,1 Hz, J = 4,2 Hz), 4,11(1H, dd, J = 8,1 Hz, J = 4,2 Hz), 2,98-2,93(1H, m), 2,59-2,54(1H, m), 2,36(6H, s), 2,17(1H, dd, J = 13 Hz, J = 6,6 Hz), 1,97-1,88(1H, m), 1,71-1,54(3H, m)
VIII-31		9,92(1H, s), 8,62(1H, s l), 8,58(1H, s), 8,22(1H, d, J = 6,9 Hz), 7,96(1H, s l), 7,76(1H, d, J = 6,6 Hz), 7,70(1H, d, J = 6,6 Hz), 7,50-7,45(1H, m), 7,35-7,28(3H, m), 7,19(1H, t, J = 6,6 Hz), 5,27(2H, s), 4,18(1H, dd, J = 7,8 Hz, J = 4,5 Hz), 4,06(1H, dd, J = 7,8 Hz, J = 4,5 Hz), 3,43(1H, t, J = 4,8 Hz), 3,24(3H, s), 3,08-2,99(2H, m), 2,88-2,81(1H, m), 2,36(3H, s), 2,27(1H, dd, J = 13 Hz, J = 6,6 Hz), 1,93-1,84(1H, m), 1,72-1,54(3H, m)

Quadro 20

Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-40		10,08(1H, sl), 8,74(1H, s), 8,58(1H, s), 8,21(1H, d, J = 8,8 Hz), 7,96(1H, s), 7,80(1H, d, J = 8,8 Hz), 7,51-7,45(1H, m), 7,35-7,27(3H, m), 7,19(1H, t, J = 8,0 Hz), 5,27(2H, s), 4,04(2H, t, J = 5,6 Hz), 3,08-3,05(1H, m), 2,22(3H, s), 1,04(3H, d, J = 6,4 Hz).
VIII-41		10,13-10,09(1H, m), 8,82(1H, s), 8,74(1H, s), 8,21(1H, d, J = 14,0 Hz), 7,69-7,62(1H, m), 7,50-7,45(1H, m), 7,35-7,26(3H, m), 7,18(1H, t, J = 8,2 Hz), 5,27(2H, s), 4,69(1H, sl), 4,25-4,21 (1H, m), 4,13-4,09(1H, m), 3,46-3,44(2H, m), 3,09(1H, t, J = 5,6 Hz), 2,26(3H, s)
VIII-42		10,2(1H, s), 8,78(1H, s), 8,59(1H, s), 8,24(1H, d, J = 8,8 Hz), 7,96(1H, s), 7,81(1H, d, J = 8,8 Hz), 7,66-7,73(1H, m), 7,43-7,50(1H, m), 7,23-7,36(3H, m), 7,15-7,22(1H, m), 5,27(2H, s), 4,31-4,48(2H, m), 3,07-3,15(2H, m), 2,27(3H, s)
VIII-43		10,10(1H, s l), 8,75(1H, d, J = 2,0 Hz), 8,59(1H, s), 8,17(1H, dd, J = 2,4, 11,6 Hz), 7,96(1H, d, J = 3,2 Hz), 7,80(1H, d, J = 12,0 Hz), 7,68(1H, dd, J = 3,6, 12,0 Hz), 7,51-7,44(1H, m), 7,34-7,26(3H, m),7,22-7,15(1H, m), 5,27(2H, s), 4,94(2H, s), 3,71(3H, s), 2,27(3H, s)

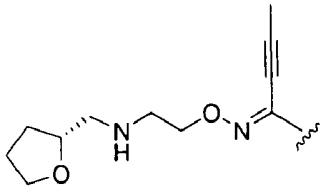
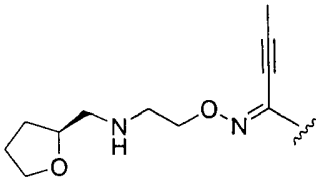
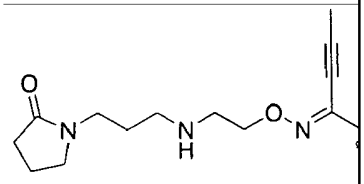
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Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-44		(CDCl3) 8,71(1H, s), 8,53(1H, s), 8,39(1H, s), 8,23(1H, d, J = 9,0 Hz), 7,88(1H, d, J = 9,0 Hz), 7,81(1H, d, J = 2,4 Hz), 7,57(1H, dd, J = 2,4, 9,0 Hz), 7,40-7,33(1H, m), 7,26-7,21(2H, m), 7,06-6,97(2H, m), 5,17(2H, s), 4,49(2H, t, J = 5,4 Hz), 3,40(2H, d, J = 6,0 Hz), 3,25(3H, s), 3,14-2,98(3H, m), 2,25(3H, s), 1,06(3H, d, J = 6,6 Hz).
VIII-45		(sal de di-HCl) 12,2(1H, s), 9,61(2H, s l), 9,38(1H, s), 8,93(1H, s), 8,46(1H, d, J = 8,8 Hz), 8,03(1H, d, J = 8,4 Hz), 7,93(1H, d, J = 2,4 Hz), 7,69(1H, dd, J = 8,8 Hz, J = 2,4 Hz), 7,44-7,52(1H, m), 7,30-7,36(3H, m), 7,15-7,23(1H, m), 5,32(2H, s), 4,61(2H, s l), 3,65-3,70(2H, m), 3,45-3,56(5H, m), 3,12(3H, s), 2,28(3H, s)
VIII-46		10,07(1H, s l), 8,73(1H, s), 8,58(1H, s), 8,21(1H, d, 6,6 Hz), 7,96(1H, s), 7,79(1H, d, J = 6,6 Hz), 7,68(1H, d, J = 6,6 Hz), 7,49-7,44(1H, m), 7,34-7,25(3H, m), 7,19-7,15(1H, m), 5,26 (2H, s), 4,31(2H, t, 4,5 Hz). 2,95(2H, t, 4,5 Hz), 2,25(3H, s), 2,16(1H, m), 0,36(2H, m), 0,25 (2H, m)
VIII-47		(sal de di-HCl) 12,26(1H, s l), 9,36(1H, s), 8,91(1H, s), 8,45(1H, d, 6,6 Hz), 8,29(1H, m), 8,00(1H, d, J = 6,6 Hz), 7,91(1H, s), 7,68(1H, d, J = 6,6 Hz), 7,51-7,45(1H, m), 7,36-7,31(3H, m), 7,23-7,17(1H, m), 5,32(2H, s), 4,59(2H, m), 3,48(2H, m), 3,41(2H, m), 3,10(2H, m), 2,28(3H, s), 1,82(3H, s)

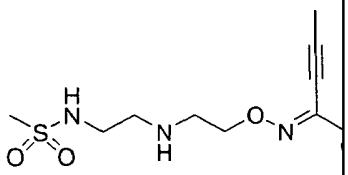
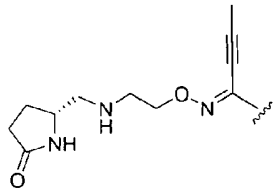
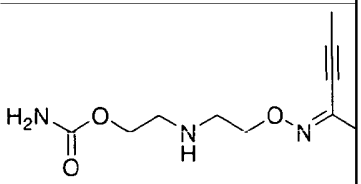
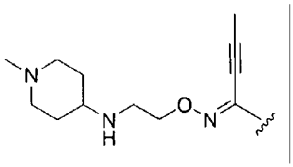
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Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)

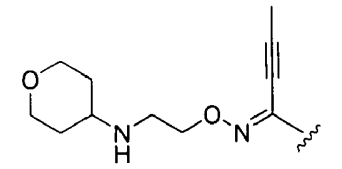
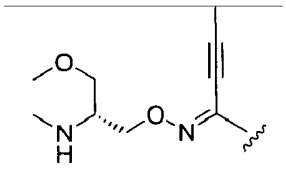
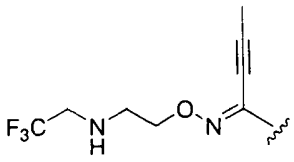
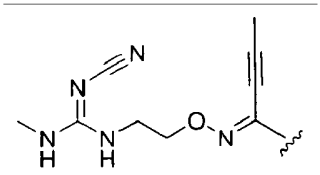
Quadro 21

Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-48		(sal de di-HCl) 12,49(1H, s l), 9,43(1H, s), 8,93(1H, s), 8,43(1H, d, 6,6 Hz), 8,09(1H, d, J = 6,6 Hz), 7,93(1H, s), 7,70(1H, d, J = 6,6 Hz), 7,51-7,45(1H, m), 7,36-7,31(3H, m), 7,23-7,17 (1H, m), 5,32(2H, s), 4,61(2H, m), 4,24(1H, m), 3,80(1H, m), 3,68(1H, m), 3,49(2H, m), 3,20(1H, m), 3,05(1H, m), 2,28(3H, s), 1,99(1H, m), 1,83(2H, m), 1,58(1H, m)
VIII-49		(sal de di-HCl) 12,44(1H, s l), 9,41(1H, s), 8,92(1H, s), 8,43(1H, d, 6,6 Hz), 8,08(1H, d, J = 6,6 Hz), 7,92(1H, s), 7,70(1H, d, J = 6,6 Hz), 7,51-7,45(1H, m), 7,36-7,31(3H, m), 7,23-7,16 (1H, m), 5,31(2H, s), 4,61(2H, m), 4,24(1H, m), 3,80(1H, m), 3,68(1H, m), 3,48(2H, m), 3,19(1H, m), 3,05(1H, m), 2,28(3H, s), 1,99(1H, m), 1,84(2H, m), 1,58(1H, m).
VIII-50		(sal de di-HCl) 12,37(1H, s l), 9,41(1H, s), 8,91(1H, s), 8,41(1H, d, 6,0 Hz), 8,04(1H, d, J = 6,0 Hz), 7,91(1H, s), 7,68(1H, d, J = 6,0 Hz), 7,45(1H, m), 7,36-7,31(3H, m), 7,20-7,14(1H, m), 5,29(2H, s), 4,58(2H, m), 3,44(2H, m), 3,31(2H, m), 3,22(2H, m), 2,95(2H, m), 2,27-1,55(9H, m)

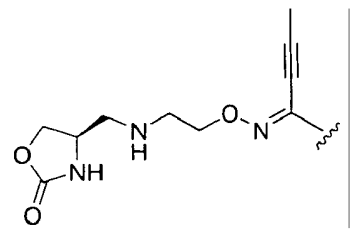
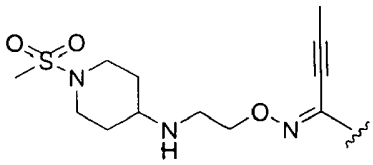
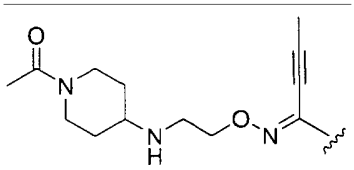
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Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-51		(sal de di-HCl) 10,07(1H, s l), 8,74(1H, s), 8,58(1H, s), 8,20(1H, d, 6,6 Hz), 7,96(1H, s), 7,79(1H, d, J = 6,6 Hz) 7,69(1H, d, J = 6,6 Hz), 7,66(1H, s), 7,49- 7,43(1H, m), 7,34-7,24(3H, m), 7,19-7,15(1H, m), 5,26(2H, s), 4,32(2H, m), 3,61(1H, m), 2,93(2H, m), 2,61(2H, d, 4,5 Hz), 2,25(3H, s), 2,09(3H, m), 1,70(1H, m)
VIII-52		10,07(1H, s l), 8,74(1H, s), 8,58(1H, s), 8,20(1H, d, 6,6 Hz), 7,96(1H, s), 7,79(1H, d, J = 6,6 Hz) 7,69(1H, d, J = 6,6 Hz), 7,66(1H, s), 7,49-7,43(1H, m), 7,34-7,24(3H, m), 7,19-7,15(1H, m), 5,26(2H, s), 4,32(2H, m), 3,61(1H, m), 2,93(2H, m), 2,61(2H, d, 4,5 Hz), 2,25(3H, s), 2,09(3H, m), 1,70(1H, m)
VIII-53		(sal de di-HCl) 12,04(1H, s l), 9,26(1H, s), 8,91(1H, s), 8,45(1H, d, 10,5 Hz), 7,99(1H, d, 9,0 Hz), 7,91(1H, s), 7,67(1H, d, J = 9,0 Hz), 7,53-7,45(1H, m), 7,37-7,31(3H, m), 7,23-7,17(1H, m), 6,65(2H, s), 5,32(2H, s), 4,58(2H, m), 4,23(2H, m), 3,50(2H, m), 3,30(2H, m), 2,28(3H, s)
VIII-54		(sal de tri-HCl) 10,88(1H, sl), 9,68(1H, sl), 9,33(1H, s), 8,83(1H, s), 8,61(1H, sl), 8,54(2H, d, J = 5,2 Hz), 8,00(1H, d, J = 7,96 Hz), 7,95(1H, s), 7,71(1H, d, J = 8,4 Hz), 7,49-7,45(1H, m), 7,33(2H, d, J = 5,6 Hz), 7,24-7,17(1H, m), 5,31(2H, s), 4,61(2H, sl), 2,91(2H, sl), 2,68(3H, s), 2,37-2,33(2H, m), 2,29(3H, s), 2,05-1,79(5H, m), 1,24(2H, s).

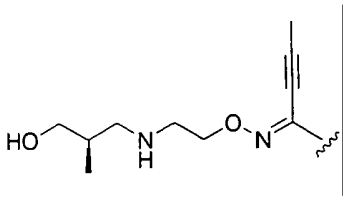
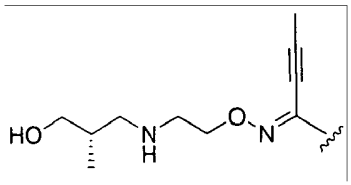
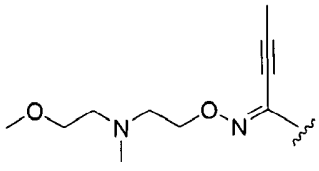
Quadro 22

Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-55		10,07(1H, sl), 8,74(1H, s), 8,59(1H, s), 8,31(1H, s), 8,21 (1H, d, J = 8,8 Hz), 7,96(1H, s), 7,80(1H, d, J = 8,4 Hz), 7,69(1H, d, J = 9,2 Hz), 7,50-7,45 (3H, m), 7,18(1H, t, J = 6,4 Hz), 5,27(2H, s), 4,33-4,30(2H, m), 3,81(2H, d, J = 7,2 Hz), 2,93 (2H, t, J = 5,9 Hz), 2,67-2,65(1H, m), 2,33(3H, s), 1,76(2H, d, J = 11,6 Hz), 1,24-1,16(4H, m).
VIII-56		10,08(1H, s), 8,75(1H, s), 8,59(1H, s), 8,21(1H, d, J = 10,0 Hz), 7,80(1H, d, J = 10,0 Hz), 7,69(1H, d, J = 8,4 Hz), 7,47(1H, t, J = 6,8 Hz), 7,35-7,17(4H, m), 5,27(2H, s), 3,29(3H, s), 3,08-2,93(1H, m), 2,41(3H, s), 2,26(3H, s).
VIII-57		10,1(1H, s), 8,75(1H, s), 8,59(1H, s), 8,22(1H, d, J = 8,4 Hz), 7,96(1H, s), 7,80(1H, d, J = 8,8 Hz), 7,69(1H, d, J = 8,8 Hz), 7,43-7,51(1H, m), 7,23-7,36(3H, m), 7,18(1H, t, J = 6,4 Hz), 5,27(2H, s), 4,33(2H, t, J = 5,6 Hz), 3,30-3,33(2H, m), 2,98-3,05(2H, m), 2,25(3H, s)
VIII-58		10,1(1H, s), 8,75(1H, s), 8,59(1H, s), 8,23(1H, d, J = 8,8 Hz), 7,96(1H, s), 7,80(1H, d, J = 8,8 Hz), 7,74(1H, d, J = 8,8 Hz), 7,43-7,50(1H, m), 7,25-7,35(3H, m), 7,18(1H, t, J = 7,6 Hz), 6,99-7,08(2H, m), 5,27(2H, s), 4,35(2H, t, J = 5,6 Hz), 3,48-3,53(2H, m), 2,68(3H, d, J = 4,4 Hz), 2,26(3H, s)

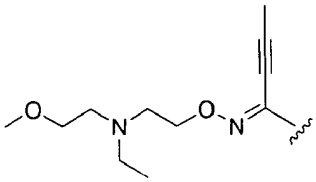
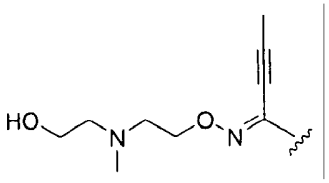
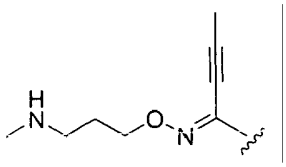
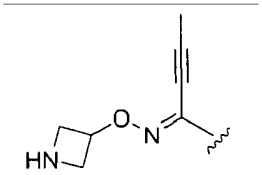
(continuação)

Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-59		(sal de di-HCl) 11,83(1H, s l), 9,02(1H, s), 8,93(1H, s), 8,45(1H, d, J = 8,7 Hz), 7,89(1H, d, 8,7 Hz), 7,87(1H, d, J = 2,4 Hz), 7,62(1H, dd, J = 2,4 Hz, J = 9,0 Hz), 7,53-7,45(1H, m), 7,38- 7,31(3H, m), 7,82-7,20(1H, m), 5,32(2H, s), 4,37(2H, m), 3,56-3,25(10H, m), 2,26(3H, s).
VIII-60		10,08(1H, s), 8,74(1H, s), 8,59(1H, s), 8,22(1H, d, J = 8,8 Hz), 7,76(1H, s), 7,81(1H, d, J = 8,8 Hz), 7,69(1H, d, J = 7,2 Hz), 7,47(1H, t, J = 7,2 Hz), 7,35-7,27(2H, m), 7,22-7,17(1H, m), 5,27(2H, s), 4,31-4,26(2H, m), 3,51-3,44(2H, m), 2,93-2,88 (2H, m), 2,83 (3H, s), 2,63-2,59(1H, m), 2,26 (3H, s), 1,91-1,88(2H, m), 1,33-1,24(2H, m).
VIII-61		10,07(1H, s), 8,75(1H, s), 8,59(1H, s), 8,21(1H, d, J = 7,2 Hz), 7,96(1H, s), 7,80(1H, d, J = 7,2 Hz), 7,69(1H, d, J = 8,8 Hz),7,48(1H, dd, J = 8,4 Hz, J = 7,2 Hz), 7,34-7,27(3H, m), 7,18(1H, t, J = 7,2 Hz), 5,27(2H, s), 4,32(2H, t, J = 6,8 Hz), 4,15(1H, sl), 3,72(1H, d, J = 12,8 Hz), 3,05(1H, t, J = 10,8 Hz), 2,94(1H, t, J = 5,6 Hz), 2,26(3H, s), 1,97(3H, s), 1,24(2H, sl).

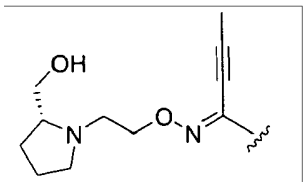
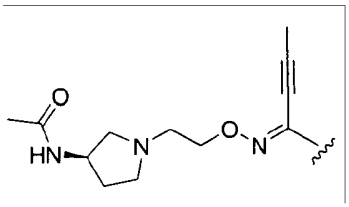
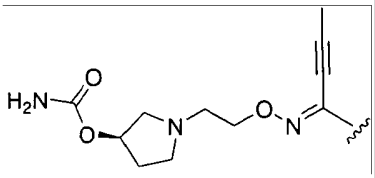
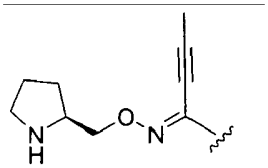
Quadro 23

Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-62		(sal de di-HCl) 12,14(1H, sl), 9,16-9,08(1H, m), 8,91(2H, s), 8,44(1H, d, J = 8,0 Hz), 8,91(2H, s), 8,44(1H, d, J = 8,0 Hz), 8,02(1H, d, J = 8,8 Hz), 7,91(1H, s), 7,68(1H, d, J = 8,4 Hz), 7,51-7,46(1H, m), 7,37-7,31(2H, m), 7,21-7,18(1H, m), 5,32(2H, s), 4,62(2H, sl), 3,44-3,38(2H, m), 3,32-3,21(2H, m), 3,08-3,07(1H, m), 2,99-2,91(1H, m), 2,28(3H, s), 2,08-2,02(1H, m), 1,24-1,19(1H, m), 0,91(3H, d, J = 6,4 Hz).
VIII-63		10,08(1H, s), 8,75(1H, s), 8,68(1H, s), 8,22(1H, d, J = 8,8 Hz), 7,79(1H, s), 7,80(1H, d, J = 7,2 Hz), 7,70(1H, d, J = 8,8 Hz), 7,50-7,45(1H, m), 7,35-7,27(3H, m), 7,18(1H, t, J = 8,8 Hz), 5,27(2H, s), 4,34(2H, t, J = 5,6 Hz), 3,35-3,32(2H, m), 2,92(2H, t, J = 5,6 Hz), 2,65-2,61(1H, m), 2,26(3H, s), 1,75-1,70(1H, sl), 0,84(3H, d, J = 5,6 Hz).
VIII-64		10,09(1H, s), 8,58(1H, s), 8,22(1H, dd, J = 8,7 Hz, 1,8 Hz), 7,95(1H, d, J = 2,7 Hz), 7,80(1H, d, J = 9,0 Hz), 7,68(1H, dd, J = 8,7 Hz, 2,7 Hz), 7,51-7,44 (1H, m), 7,35-7,16(4H, m), 3,22(3H, s), 2,77(2H, t, J = 5,7 Hz), 2,60(2H, t, J = 5,7 Hz), 2,29(3H, s), 2,24 (3H, s).

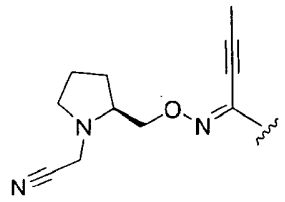
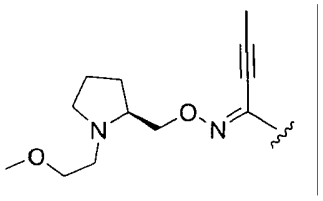
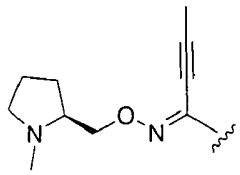
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Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-65		10,09(1H, sl), 8,74(1H, s), 8,58(1H, s), 7,96(1H, d, J = 2,1 Hz), 7,80(1H, d, J = 8,7 Hz), 7,68(1H, d, J = 9,0 Hz), 7,48 (1H, dd, J = 8,1 Hz), 7,35-7,26(3H, m), 7,19(1H, t, J = 8,1 Hz), 5,27(2H, s), 4,32(2H, t, J = 6,0 Hz), 3,23(3H, s), 2,85(2H, t, J = 6,0 Hz), 2,87-2,59(4H, m), 2,24(3H, s), 0,98(3H, t, J = 7,2 Hz).
VIII-66		(sal de di-HCl) 10,70(1H, s l), 9,92(1H, s l), 8,94(1H, s), 8,69(1H, s), 8,30(1H, d, J = 12), 7,95-7,94(1H, m), 786(1H, d, J = 12), 7,71-7,68(1H,m), 7,52-7,44(1H, m), 7,35-7,28(3H, m), 7,22-7,15(1H, m), 5,40(1H, l), 5,30(2H, s), 4,74-4,60(2H, m), 3,83-3,75(2H, m), 3,70-3,55(2H, m), 2,92(3H, s), 2,28(3H, s)
VIII-67		10,09(1H, s), 8,75(1H, s), 8,59(1H, s), 8,22(1H, d, J = 8,7 Hz), 7,95(1H, d, J = 2,1 Hz), 7,81 (1H, d, J = 9,0 Hz), 7,69(1H, d, J = 8,7 Hz), 7,51-7,34 (1H, m), 7,34-7,26(2H, m), 7,21-7,16(1H, m), 5,27(2H, s), 4,34(2H, t, J = 6,3 Hz), 2,96(2H, t,, J = 6,9 Hz), 2,56(3H, s), 2,26(3H, s).
VIII-68		10,4(1H, s), 9,06(1H, s), 8,59(1H, s), 8,30(1H, d J = 8 Hz), 8,01(1H, s), 7,81(1H, d, J = 8,8 Hz), 7,74(1H, d, J = 8,8 Hz), 7,44-7,50(1H, m), 7,24-7,36(3H, m), 7,18(1H, t, J = 7,2 Hz), 5,27(2H, s), 4,21-4,36(4H, m), 3,98-4,04(1H, m), 2,25(3H, s)

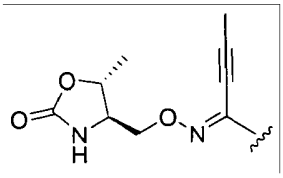
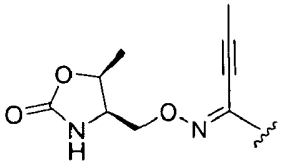
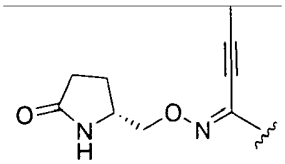
Quadro 24

Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-69		(sal de di-HCl) 9,37(1H, s), 8,91(1H, s), 8,42(1H, d, 7,8 Hz), 8,00(1H, d, J = 6,6 Hz), 7,92(1H, s), 7,69(1H, d, J = 7,8 Hz), 7,51-7,45(1H, m), 7,36-7,31(3H, m), 7,22-7,17(1H, m), 5,32(2H, s), 4,75-4,60(2H, m), 3,85-3,10(7H, m), 2,27(3H, s), 2,15-1,74(4H, m)
VIII-70		10,07(1H, sl), 8,74(1H, sl), 8,59(1H, s), 8,22 (1H, d, J = 8,8 Hz), 7,98-7,96(2H, m), 7,80(1H, d, J = 8,8 Hz), 7,68(1H, d J = 8,8 Hz), 7,50-7,45(1H, m), 7,35-7,27(3H, m), 7,20-7,16(1H, m), 5,27 (2H, s), 4,37(2H, t, J = 5,6 Hz), 4,16(1H, sl), 2,79-2,66(4H, m), 2,46-2,42(3H, m), 2,25(3H, s), 2,06(1H, sl), 1,78(3H, s), 1,56-1,51(1H, m).
VIII -71		(sal de di-HCl) 9,29(1H, m), 8,91(1H, s), 8,42 (1H, m), 7,99(1H, d, 8,7 Hz), 7,92(1H, s), 7,67 (1H, d, J = 9,0 Hz), 7,53-7,45(1H, m), 7,37-7,31 (3H, m), 7,23-7,17(1H, m), 6,68(2H, s l), 5,32(2H, s), 5,11(1H, m), 4,66(3H, m), 3,72-3,70(5H, m), 3,51(1H, m), 3,26(2H, m), 2,28(3H, s)
VIII-72		10,08(1H, sl), 8,74(1H, s), 8,56(1H, s), 8,21(1H, d, J = 8,0 Hz), 7,93(1H, s), 7,79(1H, d, J = 8,8 Hz), 7,67-7,65(1H, m), 7,50-7,40(1H, m), 7,33-7,24 (2H, m), 7,20-7,12(1H, m), 5,25(2H, s), 4,36-4,30 (1H, m), 4,22-4,17(1H, m), 4,08-3,92(2H, m), 2,98(2H, sl), 2,24(3H, s), 2,00-1,90(1H, m), 1,80-1,70(2H, m), 1,62-1,52(1H, m)

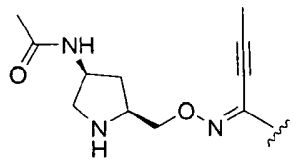
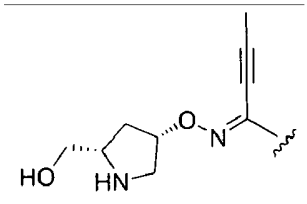
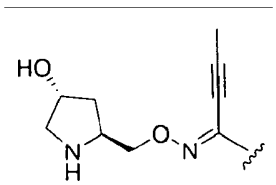
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Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-73		10,08(1H, sl), 8,80(1H, s), 8,57(1H, s), 8,21 (1H, d, J = 8,8 Hz), 7,97(1H, s), 7,79(1H, d, J = 8,8 Hz), 7,71-7,68(1H, m), 7,46(1H, dd, J = 8,0, J = 14,4), 7,34-7,25(2H, m), 7,19-7,15 (1H, m), 5,26(2H, s), 4,22-4,20(2H, m), 2,98-2,84(2H, m), 2,25(2H, s), 1,92-1,82(1H, m), 1,79-1,62(2H, m), 1,54-1,45(1H, m).
VIII-74		10,07(1H, sl), 8,74(1H, s), 8,58(1H, s), 8,21 (1H, d, J = 8,4 Hz), 7,95(1H, s), 7,79(1H, d, J = 8,8 Hz), 7,69-7,67(1H, m), 7,47(1H, dd, J = 8,4, J = 15,2), 7,34-7,26(2H, m), 7,19-7,15 (1H, m), 5,26(2H, s), 4,23-4,13(2H, m), 3,43(2H, t, J = 6,0), 3,23(3H, s), 3,11-3,03(2H, m), 2,91-2,86(1H, m), 2,53-2,47(1H, m), 2,30-2,24(1H, m), 2,24(3H, s), 1,90-1,83(1H, m), 1,72-1,67(2H, m), 1,59-1,53(1H, m).
VIII-75		10,07(1H, s), 8,73(1H, s), 8,57(1H, s), 8,20(1H, d, J = 8,8 Hz), 7,95-7,94(1H, m), 7,79(1H, d, J = 8,8 Hz), 7,68-7,63(1H, m), 7,46(1H, dd, J = 8,0, J = 14,0), 7,33-7,25(2H, m), 7,19-7,14 (1H, m), 5,26(2H, s), 4,27-4,18(2H, m), 2,95-2,92(1H, m), 2,62-2,57(1H, m), 2,41(3H, s), 2,23(3H, s), 2,19-2,15(1H, m), 1,96-1,87 (1H, m), 1,74-1,61(2H, m), 1,59-1,53(1H, m).

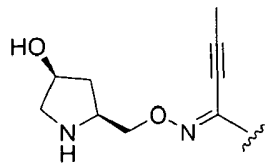
Quadro 25

Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-76		10,09(1H, sl), 8,76(1H, d, J = 1,8 Hz), 8,58(1H, s), 8,22(1H, dd, J = 1,8 Hz, J = 8,7 Hz), 7,96(1H, d, J = 2,4 Hz), 7,87-7,78(2H, m), 7,68(1H, dd, J = 2,1 Hz, J = 9,0 Hz), 7,52-7,44(1H, m), 7,35-7,26(3H, m), 7,22-7,16(1H, m), 5,27(2H, s), 4,57-4,49(1H, m), 4,35-4,27(2H, m), 3,77-3,71(1H, m), 2,26(3H, s), 1,36(3H, d, J = 6,3 Hz).
VIII-77		10,08(1H, sl), 8,75(1H, d, J = 1,8 Hz), 8,58(1H, s), 8,22(1H, dd, J = 1,8 Hz, J = 9,0 Hz), 7,96(1H, d, J = 2,4 Hz), 7,80(1H, d, J = 9,0 Hz), 7,76(1H, dd, J = 2,4 Hz, J = 9,0 Hz), 7,51-7,44(1H, m), 7,35-7,26(3H, m), 7,21-7,15(1H, m), 5,26(2H, s), 4,85-4,76(1H, m), 4,39(1H, dd, J = 5,7 Hz, J = 11,4 Hz), 4,30(1H, dd, J = 4,5 Hz, J = 11,4 Hz), 4,11-4,07(1H, m), 2,25(3H, s), 1,40(3H, d, J = 6,6 Hz).
VIII-78		10,07(1H, s l), 8,74(1H, s), 8,58(1H, s), 8,21(1H, d, 9,0 Hz), 7,97(1H, s), 7,82-7,78(2H, m), 7,69(1H, d, 9,0 Hz), 7,51-7,44(1H, m), 7,35-7,26(3H, m), 7,22-7,15(1H, m), 5,27(2H, s), 4,24(2H, d, 4,8 Hz), 3,91(1H, m), 2,31-2,06(6H, m), 1,95-1,87(1H, m)

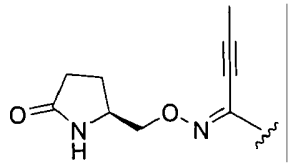
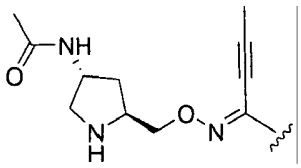
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Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-79		10,09(1H, s), 8,74(1H, s), 8,59(1H, s), 8,21(1H, d, J = 8,8 Hz), 7,97(1H, s), 7,91-7,89(1H, m), 7,80(1H. d, J = 8,4 Hz), 7,69(1H, d, J = 8,8 Hz), 7,51-7,45(1H, m), 7,35-7,27(3H, m), 7,20-7,17(1H, m), 5,27(2H, s), 4,26-4,06(3H, m), 3,46(1H, t, J = 6,8 Hz), 3,02-2,98(1H, m), 2,58(1H, dd, J = 12,0 Hz, J = 5,6 Hz), 2,26(3H, s), 2,20-2,10(1H, m), 1,77(3H, m), 1,38-1,31(1H, m).
VIII-80		10,3(1H, s), 8,95(1H, s), 8,57(1H, s), 8,22(1H, d, J = 9,6), 8,01(1H, s), 7,80- 7,73(2H, m), 7,47-7,41(1H,m), 7,34- 7,25(2H, m), 7,20-7,12(1H, m), 5,3 7(1H, l), 5,26(2H, s), 5,10(1H, s l), 3,78-3,48(5H, m), 2,45-2,35(1H, m), 2,26(3H, s), 2,05-1,96(1H, m).
VIII-81		10,45(1H, s), 8,92(1H, s), 8,65(1H, s), 8,31(1H, d, J = 8,4 Hz), 7,97(1H, s), 7,77(1H, d, J = 8,8 Hz), 7. 71(1H, d, J = 9,2 Hz), 7,51-7,45(1H, m), 7,35-7,28(2H, m), 7,19(1H, t, J = 8,4 Hz), 5,28(2H, s), 4,56-4,47(3H, m), 4,15(1H, sl), 3,60(1H, sl), 3,12(1H, sl), 2,28(3H, s), 2,09(1H, dd, J = 13,2 Hz, J = 6,0 Hz), 1,862-1,81(1H, m).

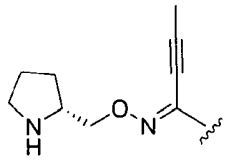
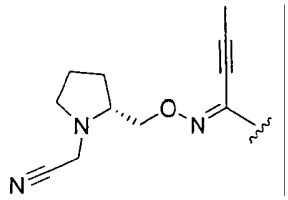
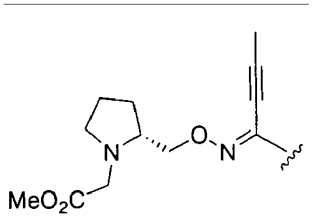
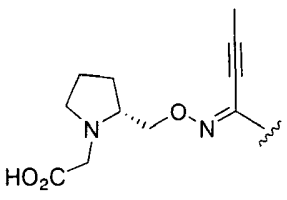
(continuação)

Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-82		10,08(1H, s), 8,75(1H, s), 8,59(1H, s), 8,22(1H, d, J = 8,8 Hz), 7,97(1H, s), 7,80(1H, d, J = 8,8 Hz), 7,69(1H, d, J = 8,0 Hz), 7,51-7,45(1H, m), 7,35-7,27(m, 3H), 7,20-7,17(1H, m), 5,27(2H, s), 4,67(1H, sl), 4,29-4,19(3H, m), 3,45-4,40(1H, m), 2,88(1H, dd, J = 11,2 Hz, J = 5,6 Hz), 2,70(1H, dd, J = 11,0, J = 3,6 Hz), 2,27(3H, s), 2,10-2,02(1H, m), 1,46-1,39(1H, m).

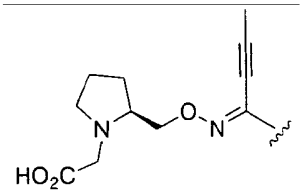
Quadro 26

Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-83		10,07(1H, s l), 8,74(1H, s), 8,58(1H, s), 8,21(1H, d, 8,7 Hz), 7,97(1H, s), 7,82-7,78(2H, m), 7,69(1H, d, 9,0 Hz), 7,51-7,44(1H, m), 7,35-7,26(3H, m), 7,22-7,15(1H, m), 5,27(2H, s), 4,24(2H, d, 4,8 Hz), 3,91(1H, m), 2,31-2,06(6H, m), 1,95-1,87(1H, m)
VIII-84		10,35(1H, s), 9,08(1H, s), 8,60(1H, s), 8,40(1H, s), 8,22(1H, d, J = 8,4 Hz), 8,09(1H, s), 7,83-7,82(2H, m), 7,49-7,47(1H, m), 7,33-7,19(4H, m), 5,27(2H, s), 4,43-4,16(4H, m), 3,01-2,98(2H,. M), 2,28(3H, s), 1,92(2H, sl), 1,83(3H, s).

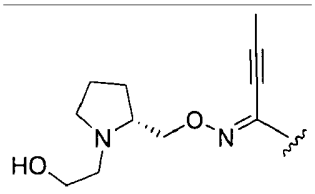
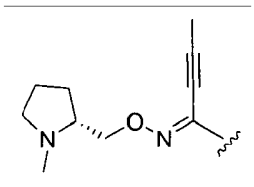
(continuação)

Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-85		10,1(1H, s l), 8,82(1H, s), 8,58(1H, s), 8,21(1H, d, J = 8,8), 7,98(1H, s), 7,80(1H, d, J = 8,4), 7,72-7,70(1H,m), 7,50-7,44(1H, m), 7,34-7,26(3H, m), 7,20-7,15(1H, m), 5,26(2H, s), 4,22(2H, s), 3,57(1H, l), 2,96-2,89(2H, m), 2,26(3H, s), 1,98-1,62(3H, m), 1,58-1,45(1H, m).
VIII -86		10,07(1H, sl), 8,75(1H, s), 8,57(1H, s), 8,21(1H, d, J = 8,8 Hz), 7,95(1H, s), 7,79(1H, d, J = 8,8 Hz), 7,71-7,68(1H, m), 7,50-7,44(1H, m), 7,34-7,26(2H, m), 7,19-7,15(1H, m), 5,26(2H, s), 4,22-4,20(2H, m), 3,03-2,95(2H, m), 2,26(3H, s), 2,02-1,93(1H, m), 1,80-1,73(2H, m), 1,62-1,56(1H, m)
VIII-87		10,0(1H, s l), 8,73(1H, s), 8,57(1H, s), 8,19(1H, d, J = 9,2), 7,95(1H, s), 7,79(1H, d, J = 8,8), 7,69-7,67(1H, m), 7,50-7,44(1H, m), 7,34-7,26(3H, m), 7,20-7,16(1H, m), 5,26(2H, s), 4,24-4,17(2H, m), 3,77(1H, d, J = 17,2), 3,58(1H, s), 3,50(1H, d, J = 17,6), 3,22-3,12(1H, m), 3,10-3,00(1H, m), 2,58-2,52(1H, m), 2,23(3H, s), 1,98-1,89(1H, m), 1,77-1,70(2H, m), 1,59-1,52(1H, m).
VIII-88		10,8(1H, s), 8,98(1H, s), 8,58(1H, s), 8,20-8,16(2H, m), 7,91-7,88(1H, m), 7,80(1H, d, J = 7,6), 7,50-7,44(1H,m), 7,34-7,30(2H, m), 7,23(1H, d, J = 8,8), 7,20-7,15(1H, m), 5,26(2H, s), 4,23-4,41(2H, m), 3,76(1H, d, J = 16,4), 3,52(1H, d, J = 16,4), 3,61-3,52(1H, m), 3,45-3,36(1H, m), 2,91-2,85(1H, m), 2,25(3H, s), 2,09-2,02(1H, m), 1,91-1,79(2H, m), 1,73-1,66(1H, m).

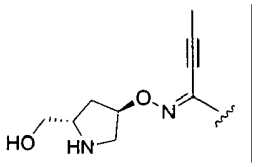
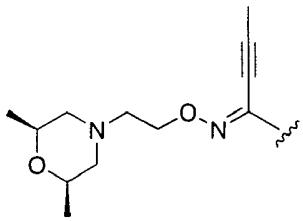
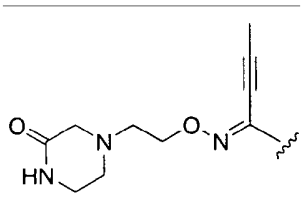
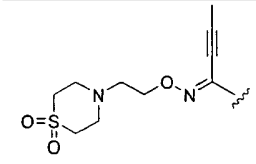
(continuação)

Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-89		10,87(1H, s), 8,97(1H, s), 8,58(1H, s), 8,20-8,15(2H, m), 7,91-7,88(1H, m), 7,80(1H, d, J = 8,8), 7,50-7,44(1H,m), 7,34-7,30(2H, m), 7,23(1H, d, J = 8,8), 7,20-7,15(1H, m), 5,26(2H, s), 4,22-4,41(2H, m), 3,76(1H, d, J = 16,4), 3,52(1H, d, J = 16,4), 3,61-3,52(1H, m), 3,45-3,36(1H, m), 2,91-2,85(1H, m), 2,25(3H, s), 2,09-2,02(1H, m), 1,91-1,79(2H, m), 1,73-1,66(1H, m).

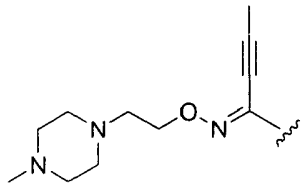
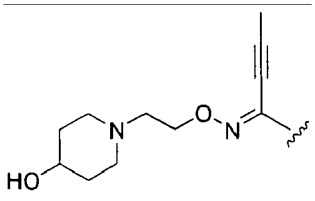
Quadro 27

Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-90		10,0(1H, s), 8,72(1H, s), 8,56(1H, s), 8,21-8,19(1H, m), 7,93(1H, s), 7,80-7,78(1H, m), 7,67-7,65(1H, m), 7,49-7,42(1H,m), 7,33-7,25(3H, m), 7,19-7,14(1H, m), 5,26(2H, s), 4,40(1H, s l), 4,27-4,19(1H, m), 4,16-4,09(1H, m), 3,10-2,94(2H, m), 2,90-2,80(1H, m), 2,23(3H, s), 1,93-1,82(1H, m), 1,75-1,62(2H, m), 1,61-1,52(1H, m).
VIII-91		10,08(1H, s), 8,74(1H, s), 8,56(1H, s), 8,21(1H, d, J = 8,8 Hz), 7,93(1H, s), 7,89(1H, d, J = 8,8 Hz), 7,68- 7,63(1H, m), 7,46(1H, dd, J = 8,0, J = 14,0), 7,33-7,24(2H, m), 7,19-7,14(1H, m), 5,25(2H, s), 4,27-4,18(2H, m), 2,95-2,92(1H, m), 2,62-2,57(1H, m), 2,41(3H, s), 2,23(3H, s), 2,46-2,39(1H, m), 2,04-1,95(1H, m), 1,78-1,73(2H, m), 1,65-1,56(1H, m)

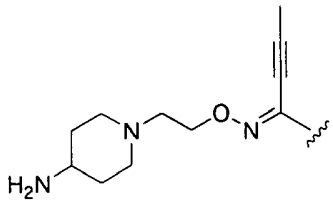
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Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-92		10,0(1H, s), 8,72(1H, s), 8,57(1H, s), 8,21(1H, d, J = 8,4), 7,94(1H, s), 7,79(1H, d, J = 8,8), 7,68-7,66(1H,m), 7,49-7,44(1H, m), 7,34-7,25(3H, m), 7,19-7,15(1H, m), 5,26(2H, s), 4,93(1H, s l), 3,02(1H, d, J = 10,7), 2,25(3H, s), 2,09-2,01(1H, m), 1,77-1,70(1H, m)
VIII -93		10,07(1H, sl), 8,74(1H, sl), 8,59(1H, s), 8,22(1H, d, J = 7,6 Hz), 7,96(1H, d, J = 2,4 Hz), 7,80(1H, d, J = 8,8 Hz), 7,69(1H, dd, J = 2,4 Hz, J = 8,8 Hz), 7,50-7,45(1H, m), 7,35-7,27(3H, m), 7,20-7,17(1H, m), 5,27(2H, s), 4,40(2H, t, J = 5,6 Hz), 3,56(2H, t, J = 8,0 Hz), 2,85(2H, t, J = 8,4 Hz), 2,69(2H, t, J = 5,6 Hz), 2,25(3H, s), 1,04(6H, d, J = 5,6 Hz).
VIII-94		10,07(1H, sl), 8,74(1H, sl), 8,59(1H, s), 8,22(1H, d, J = 8,8 Hz), 7,97(1H, d, J = 2,4 Hz), 7,80(1H, d, J = 8,8 Hz), 7,72(1H, sl), 7,69(1H, dd, J = 2,4 Hz, J = 8,8 Hz), 7,50-7,45(1H, m), 7,35-7,27(3H, m), 7,21-7,16(1H, m), 5,27(2H, s), 4,41(2H, t, J = 5,6 Hz), 3,17(2H, sl), 3,10(2H, s), 2,80(2H, t, J = 5,6 Hz), 2,70(2H, t, J = 5,6 Hz). 2,26(3H, s).
VIII-95		10,27(1H, s l), 8,74(1H, s), 8,58(1H, s), 8,23-8,21(1H, m), 7,95(1H, s), 7,80(1H, d, J = 8,8), 7,69-7,67(1H,m), 7,50-7,44(1H, m), 7,34-7,26(2H, m),7,20-7,16(1H, m), 5,27(2H, s), 4,39(2H, t, J = 5,6 Hz), 3,18(8H, s l), 2,96(2H, t, J = 5,6 Hz), 2,55(3H, s)

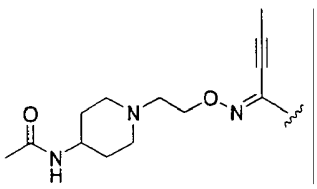
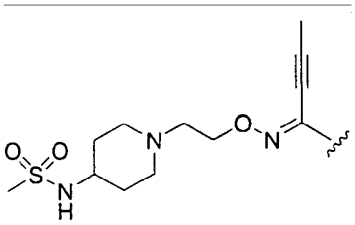
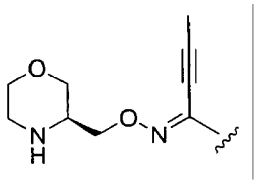
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Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-96		10,1(1H, s), 8,79(1H, s), 8,59(1H, s), 8,21(1H, d, J = 8 Hz), 7,96(1H, s), 7,79(1H, d, J = 8,8 Hz), 7,68 (1H, d, J = 8,8 Hz), 7,44-7,50(1H, m), 7,24-7,36 (3H, m), 7,18(1H, t, J = 7,2 Hz), 5,27(2H, s), 4,37 (2H, t, J = 10 Hz), 3,29-3,34(2H, m), 2,70(2H, t, J = 6,4 Hz), 2,26-2,35(4H, m), 2,25(3H, s), 2,14(3H, s)
VIII-97		1O,1(1H, s), 8,74(1H, s), 8,59(1H, s), 8,21(1H, d, J = 8,8 Hz), 7,96(1H, s), 7,80(1H, s), 7,69(1H, s), 7,42- 7,50(1H, m), 7,13-7,36(4H, m), 5,27(2H, s), 4,52(1H, s), 4,36(2H, s l), 3,40-3,50(1H, s l), 2,80(2H, s l), 2,69(2H, s l), 2,10-2,27(5H, m), 1,69(2H, s l), 1,40(2H, s l)

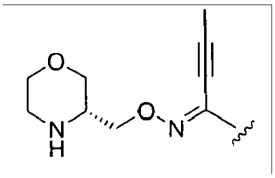
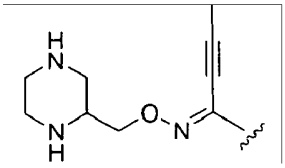
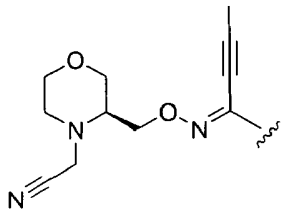
Quadro 28

Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-98		8,74(1H, s), 8,58(1H, s), 8,21(1H, d, J = 9,2 Hz), 7,96(1H, s), 7,79(1H, d, J = 9,2 Hz), 7,68(1H, d, J = 9,2 Hz), 7,48(1H, dd, J = 5,8 Hz, J = 7,2 Hz), 7,35-7,26(3H, m), 7,18(1H, t, J = 9,2 Hz), 5,27(2H, s), 4,36(2H, t, J = 9,2 Hz), 3,38(1H, dd, J = 5,8 Hz, J = 7,2 Hz), 2,86(2H, d, J = 11,6 Hz), 2,68(2H, t, J = 6,0 Hz), 2,25(3H, s), 2,06(2H, t, J = 11,2 Hz), 1,66(2H, d, J = 11,7 Hz), 1,09(2H, t, J = 7,2 Hz).

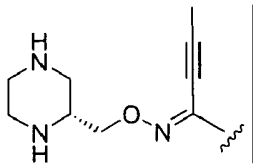
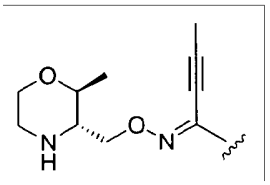
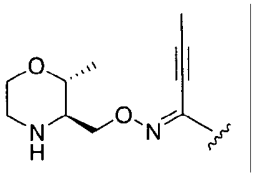
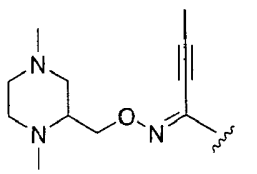
(continuação)

Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-99		10,1(1H, sl), 8,78 (1H, sl), 8,59(1H, s), 8,22(1H, d, J = 8,0 Hz), 7,97(1H, s), 7,81(1H, d, J = 8,8 Hz), 7,70(1H, d, J = 6,4 Hz), 7,49-7,45(1H, m), 5,27 (2H, s), 4,49-4,12(2H, m), 3,41-3,38(1H, m), 2,82-2,65(2H, m), 2,25(3H, s), 1,79(3H, s), 1,09(2H, t, J = 7,2 Hz).
VIII-100		10,07(1H, s), 8,74(1H, s), 8,59(1H, s), 8,21(1H, d, J = 9,2 Hz), 8,59(1H, s), 8,21(1H, d, J = 9,2 Hz), 7,96(1H, s), 7,80(1H, d, J = 8,4 Hz), 7,68(1H, d, J = 8,4 Hz), 7,50-7,45(1H, m), 7,35-7,27(3H, m), 7,19(1H, t, J = 8,0 Hz), 7,04(1H, t, J = 6,0 Hz), 5,20(2H, s), 4,30(2H, sl), 3,10(1H, sl), 2,91(3H, s), 2,63(2H, d, J = 2,4 Hz), 2,55(3H, s), 2,03-1,99(2H, m), 1,77(2H, d, J = 22,0 Hz), 1,48-1,38(2H, m), 1,24(2H, sl).
VIII-101		10,09(1H, sl), 8,75(1H, s), 8,58(1H, s), 8,20(1H, d, J = 8,7 Hz), 7,95(1H, d, J = 2,1 Hz), 7,80(1H, d, J = 8,7 Hz), 7,68(1H, d, J = 9,0 Hz), 7,51-7,44(1H, m), 7,35-7,26(3H, m), 7,21-7,16(1H, m), 5,27(2H, s), 4,20-4,09(2H, m), 3,79(1H, dd, J = 2,7 Hz, J = 10,8 Hz), 3,68-3,64(1H, m), 3,13-3,08(1H, m), 2,82-2,71(3H, m), 2,26(3H, s).

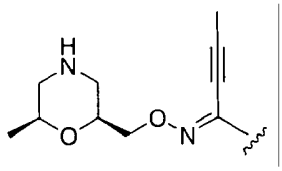
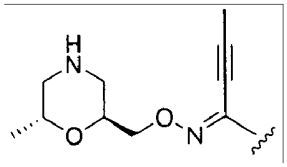
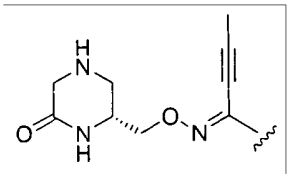
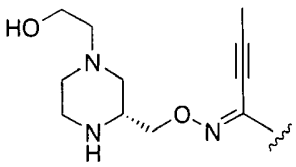
(continuação)

Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-102		10,11(1H, sl), 8,74(1H, s), 8,57(1H, s), 8,22-8,19(1H, m), 7,96(1H, m), 7,80(1H, d, J = 9,0 Hz), 7,69-7,66(1H, m), 7,51-7,44(1H, m), 7,35-7,26(3H, m), 7,21-7,16(1H, m), 5,27(2H, s), 4,20-4,09(2H, m), 3,79(1H, dd, J = 3,0 Hz, J = 10,8 Hz), 3,68-3,64(1H, m), 3,25-3,18(1H, m), 3,13-3,05(1H, m), 2,82-2,71(2H, m), 2,26(3H, s).
VIII-103		10,09(1H, s l), 8,74(1H, s), 8,59(1H, s), 8,21(1H, d, 9,0 Hz), 7,96(1H, s), 7,79(1H, d, J = 9,0 Hz) 7,68(1H, d, J = 9,0 Hz), 7,49-7,44(1H, m), 7,34-7,22 (3H, m), 7,19-7,15(1H, m), 5,27(2H, s), 4,11(2H, d, J = 4,8 Hz), 2,95-2,50(6H, m), 2,34-2,26(4H, m)
VIII-104		10,0 7(1H, s), 8,75(1H, d, J = 1,8 Hz), 8,58(1H, s), 8,22(1H, dd, J = 1,8 Hz, J = 9,0 Hz), 7,96(1H, d, J = 2,4 Hz), 7,79(1H, d, J = 8,7 Hz), 7,68(1H, dd, J = 1,8 Hz, J = 9,3 Hz), 7,51-7,44(1H, m), 7,35-7,26(3H, m), 7,21-7,15(1H, m), 5,27(2H, s), 4,35(1H, dd, J = 2,7 Hz, J = 11,7 Hz), 4,24(1H, dd, J = 3,9 Hz, J = 11,7 Hz), 4,12(1H, d, J = 17,4 Hz), 3,90-3,76(3H, m), 3,50(1H, dt, J = 2,4 Hz, J = 11,1 Hz), 2,83-2,71(2H, m), 2,26(3H, s).

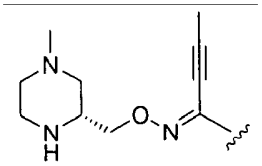
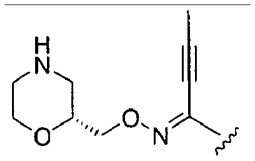
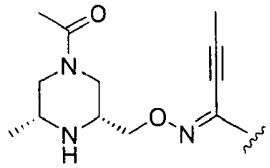
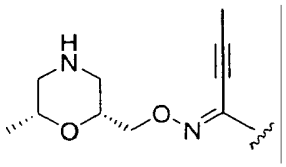
Quadro 29

Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-105		10,09(1H, s l), 8,73(1H, s), 8,58(1H, s), 8,20(1H, d, 7,8 Hz), 7,96(1H, s), 7,79(1H, d, J = 9,0 Hz), 7,69(1H, d, J = 8,4 Hz), 7,51-7,42(1H, m), 7,35-7,25(3H, m), 7,22-7,16(1H, m), 5,27(2H, s), 4,31(2H, d, 4,5 Hz), 2,95-2,53(5H, m), 2,34-2,10(5H, m)
VIII-106		10,1(1H, s), 8,75(1H, s), 8,59(1H, s), 8,21(1H, d, J = 8,8 Hz), 7,97(1H, s), 7,80(1H, d, J = 8,4 Hz), 7,69(1H, d, J = 8,8 Hz), 7,43-7,52(1H, m), 7,15-7,37(4H, m), 5,27(2H, s), 4,23-4,29(1H, m), 4,11-4,17(1H, m), 3,69(1H, d, J = 12 Hz), 3,37-3,45(1H, m), 3,23-3,32(1H, m), 2,66-2,80(3H, m), 2,28-2,40(1H, m), 2,26(3H, s), 1,16(3H, d, J = 6 Hz)
VIII-107		10,1(1H, s), 8,75(1H, s), 8,59(1H, s), 8,21(1H, d, J = 8,8 Hz), 7,97(1H, s), 7,80(1H, d, J = 8,4 Hz), 7,69(1H, d, J = 8,8 Hz), 7,43-7,52(1H, m), 7,15-7,37(4H, m), 5,27(2H, s), 4,23-4,29(1H, m), 4,11-4,17(1H, m), 3,69(1H, d, J = 12 Hz), 3,37-3,45(1H, m), 3,23-3,32(1H, m), 2,66-2,80(3H, m), 2,28-2,40(1H, m), 2,26(3H, s), 1,16(3H, d, J = 6 Hz)
VIII-108		10,09(1H, s l), 8,75(1H, s), 8,59(1H, s), 8,21(1H, d, 10,5 Hz), 7,96(1H, s), 7,80(1H, d, J = 9,0 Hz), 7,68(1H, d, J = 9,0 Hz), 7,52-7,44(1H, m), 7,35-7,25(3H, m), 7,22-7,16(1H, m), 5,27(2H, s), 4,44(1H, m), 4,18(1H, m), 2,80-2,60(4H, m), 2,32-2,00(12H, m)

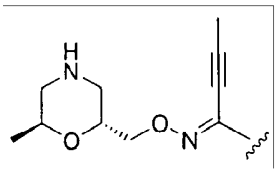
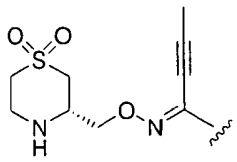
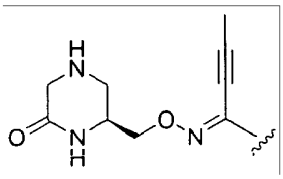
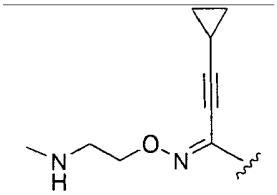
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Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-109		10,1(1H, s), 8,74(1H, s), 8,59(1H, s), 8,21(1H, d, J = 8,0 Hz), 7,96(1H, s), 7,80(1H, d, J = 8,8 Hz), 7,66-7,70(1H, m), 7,43-7,50(1H, m), 7,15-7,36(4H, m), 5,72(2H, s), 4,10-4,27(2H, m), 3,75-3,82(1H, m), 3,45-3,55(1H, m), 2,85(1H, d, J = 10 Hz), 2,74(1H, d, J = 11 Hz), 2,37(1H, t, J = 11 Hz), 2,26(4H, s l), 1,03(3H, d, J = 6,4 Hz).
VIII-110		10,1(1H, s), 8,74(1H, s), 8,58(1H, s), 8,21(1H, d, J = 8,8 Hz), 7,96(1H, s), 7,80(1H, d, J = 8,4 Hz), 7,68(1H, s, J = 9,6 Hz), 7,42-7,52(1H, m), 7,14-7,37(4H, m), 5,27(2H, s), 4,38-4,55(2H, m), 3,80-4,05(2H, m), 2,75-2,85(2H, m), 2,65-2,72(1H, m), 2,30-2,40(1H, m), 2,26(3H, s), 1,06(3H, d, J = 5 Hz)
VIII-111		10,08(1H, s), 8,74(1H, s), 8,59(1H, s), 8,20(1H, d, J = 8,7 Hz), 7,98(1H, d, J = 0,9H Hz), 7,83-7,72(2H, m), 7,10(1H, dd, J = 2,7 Hz. J = 9,0 Hz), 7,51-7,44(1H, m), 7,34-7,26(3H, m), 7,22-7,16(1H, m), 5,27(2H, s), 4,32(2H, m), 3,65(1H, m), 3,17(2H, s), 3,10-2,84(3H, m), 2,26(3H, s).
VIII-112		(sal de di-HCl) 12,03(1H, s l), 8,93(1H, s), 8,46(1H, d, J = 9,0 Hz), 8,02(1H, d, J = 8,7 Hz), 7,92(1H, d, J = 2,4 Hz), 7,68-7,67(1H, m9, 7,52-7,36(1H, m), 7,35-7,31(3H, m), 7,23-7,19(1H, m), 5,31(2H, s), 4,58(2H, m), 4,33(1H, s l), 3,99-3,23(12H, m), 2,29(3H, s).

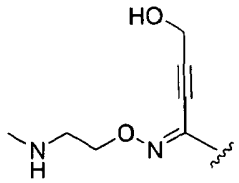
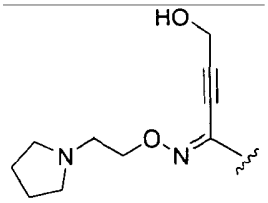
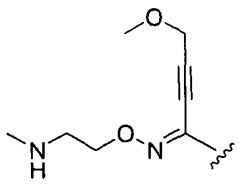
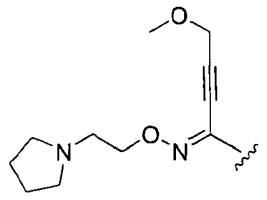
Quadro 30

Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-113		10,09(1H, s l), 8,74(1H, s), 8,58(1H, s), 8,20(1H, d, J = 8,7 Hz), 7,96(1H, d, J = 2,4 Hz), 7,79(1H, d, J = 8,7 Hz), 7,68(1H, dd, J = 2,7 Hz, J = 9,0 Hz), 7,51-7,44(1H, m), 7,36-7,16(4H, m), 5,27(2H, s), 4,15(2H, m), 3,07(1H, m), 2,87-2,55(4H, m), 2,26(3H, s),2,15(3H, s), 1,90(1H, m), 1,71(1H, m).
VIII-114		(sal de di-HCl) 11,65(1H, sl), 9,46-9,35(2H, m), 9,04(1H, s), 8,88(1H, s), 7,95(1H, d, J = 9,0 Hz), 7,89(1H, d, J = 2,4 Hz), 7,66-7,62(1H, m), 7,52-7,45(1H, m), 7,36-7,31(3H, m), 7,23-7,17(1H, m), 5,31(2H, s), 4,35-4,34(2H, m), 4,24-4,21(1H, m), 4,04-3,98(1H, m), 3,85-3,77(1H, m), 3,05-2,85(3H, m), 2,28(3H, s).
VIII-115		
VIII-116		10,1(1H, s), 8,74(1H, s), 8,59(1H, s), 8,21(1H, d, J = 8,0 Hz), 7,96(1H, s), 7,80(1H, d, J = 8,8 Hz), 7,66-7,70 (1H, m), 7,43- 7,50(1H, m), 7,15-7,36(4H, m), 5,72(2H, s), 4,10-4,27(2H, m), 3,75-3,82(1H, m), 3,45-3,55(1H, m), 2,85(1H, d, J = 10 Hz), 2,74(1H, d, J = 11 Hz); 2,37(1H, t, J = 11 Hz), 2,26(4H, s l), 1,03(3H, d, J = 6,4 Hz).

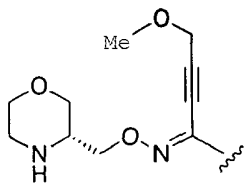
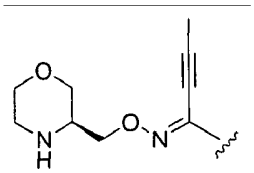
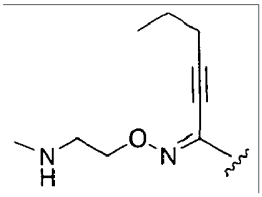
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Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-117		10,1(1H, s), 8,74(1H, s), 8,58(1H, s), 8,21(1H, d, J = 8,8 Hz), 7,96(1H, s), 7,80(1H, d, J = 8,4 Hz), 7,68(1H, s, J = 9,6 Hz), 7,42-7,52(1H, m), 7,14-7,37(4H, m), 5,27(2H, s), 4,38-4,55(2H, m), 3,80-4,05(2H, m), 2,75-2,85(2H, m), 2,65-2,72(1H, m), 2,30-2,40(1H, m), 2,26(3H, s), 1,06(3H, d, J = 5 Hz)
VIII-118		10,10(1H, s), 8,76(1H, s), 8,59(1H, s), 8,22(1H, d, J = 8,7 Hz), 7,96(1H, d, J = 2,1 Hz), 7,81(2H, d, J = 8,7 Hz), 7,69(1H, dd, J = 2,1 Hz, J = 8,7 Hz), 7,44-7,52(1H, m), 7,27-7,35(2H, m), 7,16-7,22(1H, m), 5,27(2H, s), 4,20-4,35(2H, m), 3,84-3,98(1H, m), 2,85-3,15(6H, m), 2,28(3H, m).
VIII-119		(sal de di-HCl) 9,14(1H, s), 8,91(1H, s), 8,61-8,55(1H, m), 8,41(1H, d, J = 9,0 Hz), 8,22(1H, d, J = 9,0 Hz), 8,00-7,9(1H, m), 7,91(1H, s), 7,66(1H, d, J = 9,0 Hz), 7,52-7,45(1H, m), 7,37-7,30(3H, m), 7,23-7,17(1H, m), 5,32(2H, s), 4,40(2H, m), 4,18(1H, m), 3,65-3,20(4H, m), 2,287(3H, s)
VIII-120		10,1(1H, s), 8,71(1H, s), 8,59(1H, s), 8,16(1H, d, J = 8,8 Hz), 7,98(1H, s), 7,80(1H, d, J = 9,2 Hz), 7,69(1H, d, J = 9,2 Hz), 7,44-7,51(1H, m), 7,14-7,36(4H, m), 5,27(2H, s), 4,31(2H, t, J = 5,6 Hz), 2,85(2H, t, J = 5,6 Hz), 2,35(3H, s), 1,70-1,78(1H, m), 1,02-1,07(2H, m), 0,90-0,95(2H, m)

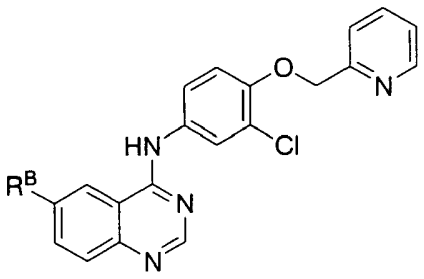
Quadro 31

Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-121		10,1(1H, s), 8,82(1H, s), 8,61(1H, s), 8,27(1H, d, J = 7,6 Hz), 7,97(1H, s), 7,84(1H, d, J = 9,6 Hz), 7,70(1H, d, J = 7,6 Hz), 7,43-7,51(1H, m), 7,25-7,36(3H, m), 7,15-7,22(1H, m), 5,62(1H, s), 5,72(2H, s), 4,49-4,55(4H, m), 3,29-3,40(2H, m), 2,66(3H s)
VIII-122		10,05(1H, s), 8,76(1H, s), 8,60(1H, s), 8,20(1H, d, J = 9,2 Hz), 7,97(1H, s), 7,82(1H, d, J = 8,8 Hz), 7,68(1H, d, J = 9,2 Hz), 7,53-7,45(1H, m), 7,37-7,27(3H, m), 7,19(1H, t, J = 8,4 Hz), 5,63(1H, t, J = 5,2 Hz), 5,27(2H, s), 4,70(2H, d, J = 5,2 Hz), 4,40(2H, t, J = 6,0 Hz), 2,81(2H, t, J = 6,0 Hz), 2,53(4H, sl), 1,68(4H, sl).
VIII-123		10,02 (1H, s), 8,89 (1H, s), 8,60(1H, s), 8,22(1H, d, J = 9,3 Hz), 8,00(1H, s), 7,83(1H, d, J = 8,7 Hz), 7,73(1H, d, J = 9,6 Hz), 7,51-7,44(1H, m), 7,35-7,29(2H, m), 7,22-7,16(1H, m), 5,2782H, s), 4,53(2H, s), 3,40(5H, sl), 2,51(5H, sl).
VIII-124		10,13(1H, s), 8,80(1H, s), 8,61(1H, s), 8,21(1H, d, J = 8,4 Hz), 7,99(1H, s), 7,83(1H, d, J = 8,8 Hz), 7,71(1H, d, J = 8,8 Hz), 7,51- 7,45(1H, m), 7,35-7,27(3H, m), 7,19(1H, t, J = 8,4 Hz), 5,27(2H, s), 4,53(2H, s), 4,46(2H, t, J = 5,6 Hz), 2,93(2H, sl), 2,65(4H, sl), 1,72(4H, sl).

(continuação)

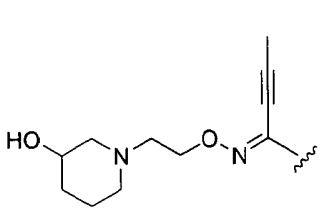
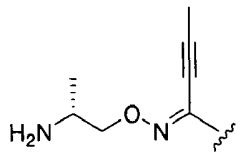
Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-125		10,09(1H, s), 8,76(1H, sl), 8,59(1H, s), 8,19(1H, d, J = 9,0 Hz), 7,96(1H, sl), 7,82(1H, d, J = 8,7 Hz), 7,67(1H, dl, J = 7,5 Hz), 7,51-7,44(1H, m), 7,35-7,26(3H, m), 7,21-7,16(1H, m), 5,27(2H, s), 4,52(2H, s), 4,23(1H, dd, J = 5,7 Hz, J = 10,8 Hz), 4,17(1H, dd, J = 6,3 Hz, J = 10,8 Hz), 3,79(1H, dd, J = 3,0 Hz, J = 10,8 Hz), 3,65(1H, dl, J = 7,8 Hz), 3,40(3H, s), 3,27-3,20(1H, m), 3,13-3,04(1H, m).
VIII-126		10,10(1H, sl), 8,76(1H, d, J = 1,5 Hz), 8,59(1H, s), 8,19(1H, dd, J = 1,8 Hz, J = 8,7 Hz), 7,96(1H, d, J = 2,1 Hz), 7,83(1H, d, J = 9,0 Hz), 7,71-7,64(1H, m), 7,52-7,44(1H, m), 7,35-7,27(3H, m), 7,22-7,16(1H, m), 5,27(2H, s), 4,53(2H, s), 4,23(1H, dd, J = 6,3 Hz, J = 11,4 Hz), 4,17(1H, dd, J = 6,3 Hz, J = 10,8 Hz), 3,80(1H, dd, J = 3,0 Hz, J = 10,8 Hz), 3,68-3,64(1H, m), 3,12-3,07(1H, m), 2,82-2,70(2H, m).
VIII-127		10,1(1H, s), 8,76(1H, s), 8,59(1H, t, J = 5,6 Hz), 8,20(1H, d, J = 8,8 Hz), 7,98(1H, s), 7,81(1H, d, J = 8,8 Hz), 7,70(1H, d, J = 8,8 Hz), 7,44-7,51(1H, m), 7,15-7,37(4H, m), 5,27(2H, s), 4,34(2H, t, J = 6 Hz), 2,86(2H, t, J = 5,6 Hz), 2,61(2H, t, J = 7,2 Hz), 2,36(3H, s), 1,67(2H, q, J = 7,2 Hz), 1,05(3H, t, J = 7,2 Hz)

Fórmula química 82

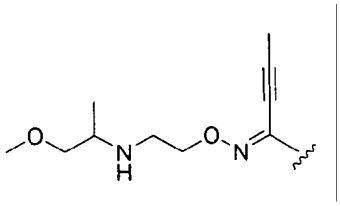
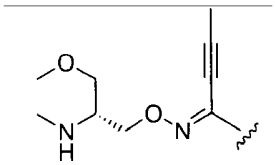
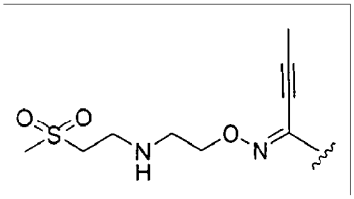


(VIII)

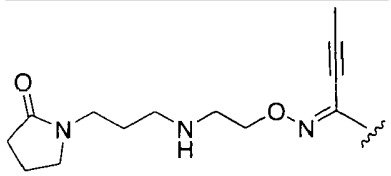
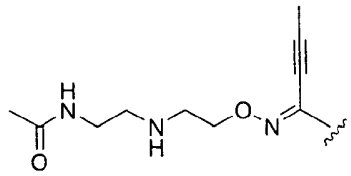
Quadro 32

N° do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-128		10,0(1H, s), 8,74(1H, s), 8,60-8,58(2H, m), 8,21(1H, d, J = 8,8), 7,96(1H, s), 7,90-7,86(1H, m), 7,79(1H, d, J = 8,8), 7,68-7,66(1H, m), 7,58 (1H, d, J = 7,6), 7,38-7,35(1H, m), 7,27(1H, d, J = 8,8), 5,30(2H, s), 4,61-4,60(1H, m), 4,37-4,35 (2H, m), 3,52-3,38(1H, m), 2,93-2,92(1H, m), 2,76-2,66(2H, m), 2,24(3H, s), 2,00-1,95(1H, m), 1,89-1,84(1H, m), 1,79-1,77(1H, m), 1,62-1,59 (1H, m), 1,45-1,36(1H, m), 1,10-1,02(1H, m).
VIII-129		10,09(1H, s), 8,61-8,59(2H, m), 8,21(1H, d, J = 9,2 Hz), 8,07(1H, s), 7,89(1H, d, J = 7,6 Hz), 7,80(1H, d, J = 8,4 Hz), 7,68(1H, d, J = 9,2 Hz), 7,37(1H, t, J = 7,6 Hz), 7,28(1H, d, J = 8,8 Hz), 5,31(2H, s), 4,60(2H, d J = 6,0 Hz), 2,27(3H, s), 0,89(3H, d, J = 7,6 Hz).

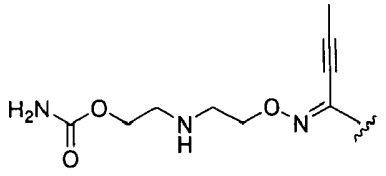
(continuação)

Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-130		(sal de tri-HCl) 12,58(1H, s), 9,44(1H, s), 9,33(1H, sl), 9,09(1H, sl), 8,95(1H, s), 8,78(1H, d, J = 4,4 Hz), 8,46(1H, d, J = 8,8 Hz), 8,23 (1H, t, J = 6,8 Hz), 8,09(1H, d, J = 8,4 Hz), 7,94 (1H, d, J = 2,4 Hz), 7,86(1H, d, J = 8,0 Hz), 7,72-7,67(2H, m), 7,39(1H, d, J = 9,2 Hz), 5,51(2H, s), 4,61 (2H, sl), 3,61-3,47(5H, m), 2,28(3H, s), 1,28(3H, d, J = 6,4 Hz).
VIII-131		10,0(1H, s), 8,74(1H, s), 8,60-8,58(2H, m), 8,20(1H, d, J = 8,8), 7,97(1H, s), 7,90-7,86(1H,m), 7,79(1H, d, J = 8,4), 7,69-7,67(1H, m), 7,58(1H, d, J = 7,6), 7,38-7,35(1H, m), 7,27(1H, d, J = 9,2), 5,30(2H, s), 4,24-4,23(2H, m), 3,44-3,34(2H, m), 2,97-2,92(1H, m), 2,38(3H, s), 2,26(3H, s).
VIII-132		10,08(1H, s), 8,98(1H, s), 8,61-8,59(2H, m), 8,23(1H, d, J = 8,8 Hz), 7,98(1H, s), 7,89(1H, t, J = 7,2 Hz), 7,80(1H, d, J = 8,8 Hz), 7,69(1H, d, J = 9,2 Hz), 7,59(1H, t, J = 8,0 Hz), 7,37(1H, d, J = 7,6 Hz), 7,28(1H, d, J = 8,8 Hz), 5,31(2H, s), 4,33(2H, t J = 4,8 Hz), 3,26(2H, t, J = 6,4 Hz), 3,03(5H, sl), 2,94(2H, sl), 2,26(3H, s).

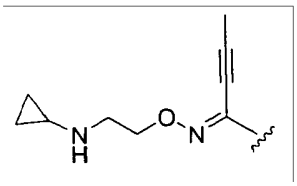
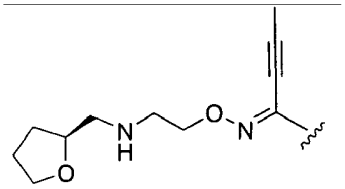
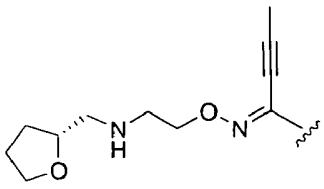
(continuação)

Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-133		10,0(1H, s), 8,74(1H, s), 8,60-8,58(2H, m), 8,21(1H, d, J = 8,0), 7,97(1H, m), 7,90-7,86(1H, m), 7,80(1H, d, J = 8,8), 7,69-7,67(1H, m), 7,59(1H, d, J = 8,0), 7,38-7,35(1H, m), 7,28(1H, d, J = 9,2), 5,30(2H, s), 4,32-4,29(2H, m), 3,22-3,18(2H, m), 2,90-2,87(2H, m), 2,57-2,53(2H, m), 2,25(3H, s), 2,20-2,16(2H, m), 1,91-1,84(2H, m), 1,62-1,55(1H, m)
VIII-134		10,11(1H, s l), 8,75(1H, s), 8,61-8,59(2H, m), 8,22(1H, d, J = 9,0 Hz), 7,91-7,78(3H, m), 7,67(1H, d, J = 9,0 Hz), 7,59(1H, d, J = 7,8 Hz), 7,40-7,36(1H, m), 7,29(1H, d, J = 9,0 Hz), 5,31(2H, s), 4,32(2H, m), 3,13(2H, m), 2,93(2H, m), 2,66(2H, m), 2,26(3H, s), 1,78(3H, s)

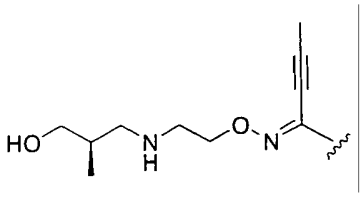
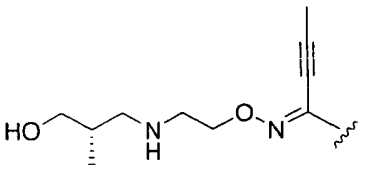
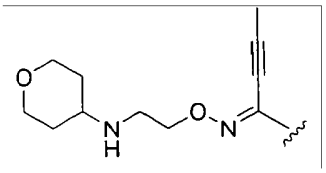
Quadro 33

Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-135		10,09(1H, s l), 8,75(1H, s), 8,61-8,59(2H, m), 8,22(1H, d, J = 9,0 Hz), 7,97(1H, s), 7,92-7,86 (1H, m), 7,81(1H, d, J = 9,0 Hz), 7,69(1H, d, J = 9,0 Hz), 7,59(1H, d, J = 7,8 Hz), 7,40-7,36(1H, m), 7,29(1H, d, J = 9,0 Hz), 6,47(2H, s l), 5,31(2H, s), 4,34(2H, m), 3,99(2H, m), 2,99(2H, m), 2,84(2H, m), 2,26(3H, s)

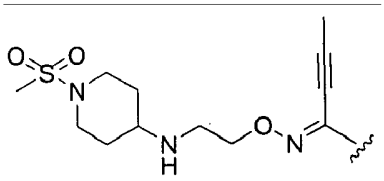
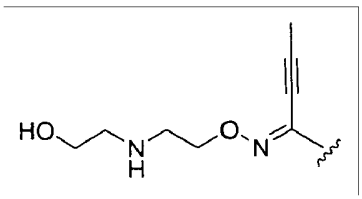
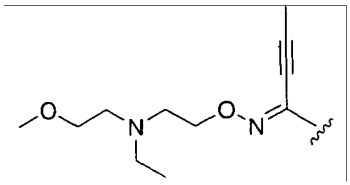
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Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-136		10,10(1H, s l), 8,75(1H, s), 8,61-8,59(2H, m), 8,22(1H, d, J = 9,0 Hz), 7,97(1H, s), 7,92-7,86 (1H, m), 7,81(1H, d, J = 9,0 Hz), 7,69(1H, d, J = 9,0 Hz), 7,59(1H, d, J = 7,8 Hz), 7,40-7,36(1H, m), 7,29(1H, d, J = 9,0 Hz), 5,31(2H, s), 4,33 (2H, t, 6,0 Hz), 3,00(2H, t, 6,0 Hz), 2,25(3H, s), 2,23(1H, m), 0,408(2H, m), 0,29(2H, m)
VIII-137		(sal de tri-HCl) 12,14(1H, s l), 9,28(1H, s), 8,93(1H, s), 8,64(1H, d, J = 4,2 Hz), 8,44(1H, d, J = 10,5 Hz), 8,02-7,91(3H, m), 7,69-7,62(1H, m), 7,46-7,42(1H, m), 7,37(1H, d, 9,0 Hz), 5,38(2H, s), 4,59(2H, m), 4,19(1H, m), 3,81(1H, m), 3,71(1H, m), 3,47(2H, m), 3,21(1H, m), 3,02(1H, m), 2,28(3H, s), 2,02(1H, m), 1,84(2H, m), 1,56(1H, m)
VIII-138		(sal de tri-HCl) 9,28(1H, s), 8,93(1H, s), 8,64(1H, d, J = 4,2 Hz), 8,44(1H, d, J = 10,5 Hz), 8,02-7,91 (3H, m), 7,69-7,62(1H, m), 7,46-7,42(1H, m), 7,37(1H, d, 9,0 Hz), 5,38(2H, s), 4,59(2H, m), 4,19(1H, m), 3,81(1H, m), 3,71(1H, m), 3,47(2H, m), 3,21(1H, m), 3,02(1H, m), 2,28(3H, s), 2,02(1H, m), 1,84(2H, m), 1,56(1H, m)

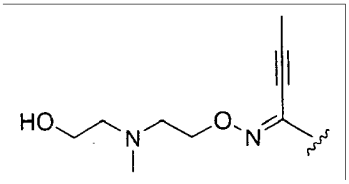
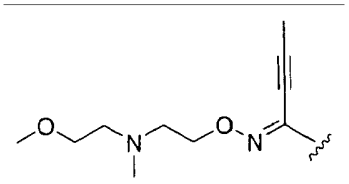
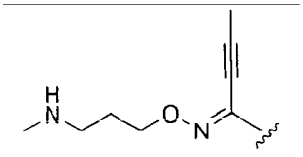
(continuação)

Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-139		10,08(1H, s), 8,75(1H, s), 8,61-8,58(2H, m), 8,22(1H, d, J = 8,8 Hz), 7,98(1H, s), 7,89(1H, t, J = 8,0 Hz), 7,68 (1H, d, J = 8,4 Hz), 7,37(1H, t, J = 6,4 Hz), 7,37(1H, t, J = 6,4 Hz), 7,28(1H, d, J = 8,4 Hz), 5,31(2H, s), 4,34(2H, t, J = 6,4 Hz), 3,33(1H, t, J = 6,4 Hz), 2,92(2H, t, J = 5,2 Hz), 2,65-2,61(1H, m), 2,26(3H, s), 1,75-1,70(1H, m), 0,83(3H, d, J = 6,8 Hz).
VIII-140		10,09(1H, s), 8,75(1H, s), 8,59(2H, sl), 8,22(1H, d, J = 8,8 Hz), 7,98(1H, s), 7,89(1H, t, J = 6,4 Hz), 7,80(1H, d, J = 8,8 Hz), 7,69(1H, t, J = 8,4 Hz), 7,59 (1H, t, J = 8,4 Hz), 7,37(1H, d, J = 5,2 Hz), 7,28(1H, d, J = 8,8 Hz), 5,31(2H, s), 4,34(2H, t, J = 6,4 Hz), 3,32(2H, t, J = 6,4 Hz), 2,92(2H, t, J = 5,6 Hz), 2,65-2,61(1H, m), 2,26(3H, s), 1,75-1,68(1H, m), 1,24(1H, sl), 0,83(3H, d, J = 6,8 Hz).
VIII-141		(sal de tri-HCl) 12,48(1H, s), 9,48(1H, s), 9,42(1H, sl), 9,29(2H, sl), 8,94(1H, s), 8,72(1H, s), 8,47 (1H, s), 8,13-8,06 (1H, m), 7,92(1H, s), 7,76(1H, sl), 7,68(1H, sl), 7,59(1H, sl), 7,39(1H, sl), 5,46(2H, s), 4,62 (2H, sl), 3,88(4H, sl), 2,28(3H, s), 2,01-1,94(4H, m), 1,69-1,60(4H, m).

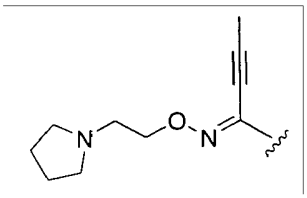
Quadro 34

Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-142		10,07(1H, s), 8,74(1H, s), 8,59(2H, s), 8,20(1H, sl), 7,97(1H, s), 7,89(1H, sl), 7,80(1H, d, J = 8,0 Hz), 7,68 (1H, sl), 7,58(1H, d, J = 8,8 Hz), 7,38(1H, sl), 7,28(1H, d, J = 9,2 Hz), 5,31(2H, s), 4,31(2H, sl), 3,45(2H, sl), 2,94(2H, sl), 2,85-2,81(5H, m), 2,26(3H, s), 1,89-1,85(2H, m), 1,36-1,28(2H, m).
VIII-143		10,09(1H, s l), 8,74(1H, s), 8,61-8,59(2H, m), 8,22(1H, d, J = 9,0 Hz), 7,97(1H, s), 7,92-7,86(1H, m), 7,81(1H, d, J = 9,0 Hz), 7,69(1H, d, J = 9,0 Hz), 7,59(1H, d, J = 7,8 Hz), 7,40-7,36(1H, m), 7,29(1H, d, J = 9,0 Hz), 5,31(2H, s), 4,23(2H, t, 5,4 Hz), 3,47(2H, t, 5,4 Hz)), 2,91(2H, t, 5,4 Hz), 2,65(2H, m), 2,25(3H, s)
VIII-144		(sal de tri-HCl) 12,4(1H, s), 10,5(1H, s), 9,34(1H, s), 8,93(1H, s), 8,68-8,67(1H, m), 8,45(1H, d, J = 9,2), 8,05-8,02(2H, m), 7,92-7,91(1H, m), 7,71-7,66(2H, m), 7,52-7,49(1H, m), 7,37(1H, d, J = 8,8), 5,41(2H, s), 4,73-4,67(1H, m), 3,30(6H, s), 2,27(3H, s),1,29-1,25(1H, m).

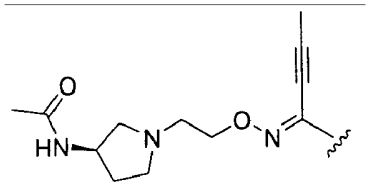
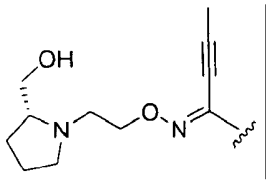
(continuação)

Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-145		10,08(1H, s), 8,75(1H, s), 8,59(2H, sl), 8,22(1H, d, J = 8,4 Hz), 7,98(1H, sl), 7,89(1H, t, J = 8,0 Hz), 7,80(1H, d, J = 9,2 Hz), 7,68 (1H, d, J = 8,8 Hz), 7,38(1H, d, J = 6,4 Hz), 7,28(1H, d, J = 8,8 Hz), 5,31(2H, s), 4,36(4H, t J = 6,4 Hz), 3,49(2H, sl), 2,79(2H, t, J = 6,0 Hz), 2,30(3H, s), 2,25(3H, s).
VIII-146		(sal de tri-HCl) 12,70(1H, s), 10,83(1H, sl), 9,49(1H, s), 8,95(1H, s), 8,77(1H, sl), 8,44(1H, d, J = 8,84 Hz), 8,23 (1H, sl), 8,10(1H, d, J = 8,8 Hz), 7,95(1H,s), 7,85(1H, d, J = 6,8 Hz), 7,74-7,68(2H, m), 7,39(1H, d, J = 8,4 Hz), 5,51(2H, s), 4,70 (2H, sl), 7,75-7,42(4H, m), 3,48-3,44(1H, m), 3,40(1H, sl), 3,30(3H, s), 2,90(3H, s), 2,28(3H, s).
VIII-147		10,28-10,03(1H, m), 8,75(1H, s), 8,61-8,58(2H, m), 8,21(1H, d, J = 8,8 Hz), 7,98(1H, s), 7,89(1H, t, J = 8,0 Hz), 7,79(1H, d, J = 7,2 Hz), 7,68(1H, d, J = 8,0 Hz), 7,37(1H, t, J = 6,0 Hz), 7,28(1H, t, J = 8,8 Hz), 5,31(2H, s), 4,33(2H, t J = 6,4 Hz), 2,31(3H, s), 2,06(3H, s), 1,88(2H, t, J = 6,4 Hz).

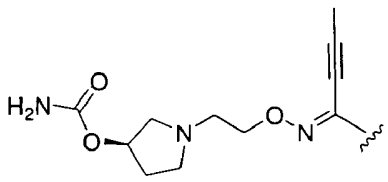
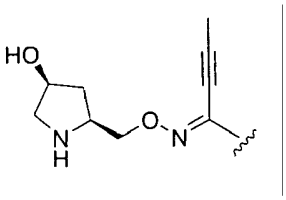
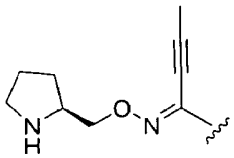
(continuação)

Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-148		10,09(1H, s l), 8,75(1H, s), 8,61-8,57(2H, m), 8,22(1H, d, J = 9,0 Hz), 7,98(1H, s), 7,92-7,86(1H, m), 7,80(1H, d, J = 9,0 Hz), 7,68(1H, d, J = 9,0 Hz), 7,59(1H, d, J = 7,8 Hz), 7,40-7,36(1H, m), 7,28(1H, d, J = 9,0 Hz), 5,31(2H, s), 4,37(2H, m), 2,82(2H, m), 2,54(4H, m), 2,25(3H, s), 1,69(4H, m)

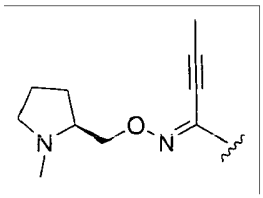
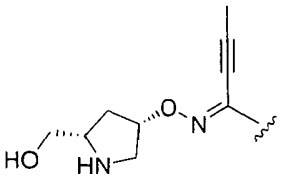
Quadro 35

Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-149		10,09(1H, s), 8,75(1H, s), 8,70(2H, s), 8,20(1H, d, J = 8,0 Hz), 8,07(2H, s), 7,98(1H, t, J = 4,8 Hz), 7,88(1H, t, J = 8,0 Hz), 7,68(1H, d, J = 8,0 Hz), 7,38(1H, s), 7,28(1H, d, J = 9,6 Hz), 5,31(2H, s), 4,42(2H, s), 4,29-4,24(1H, m), 2,91-2,76(2H, m), 2,25(3H, s), 2,17-2,12(1H, m), 1,75(3H, s), 1,53-1,34(1H, m), 1,11(2H, d, J = 4,4 Hz).
VIII-150		10,09(1H, s), 8,75(1H, s), 8,59(2H, s), 8,21(1H, sl), 7,98(1H, s), 7,89(1H, s), 7,79(1H, s), 7,68(1H, s), 7,58(1H, s), 7,37(1H, s), 7,28(1H, s), 5,31(2H, s), 4,36(2H, sl), 2,71(2H, sl), 2,25(3H, s), 1,81(1H, sl), 1,66(2H, sl), 1,52(1H, sl), 1,24(2H, sl).

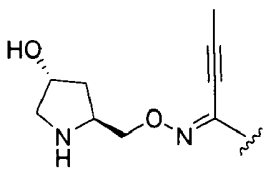
(continuação)

Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-151		10,09(1H, s l), 8,75(1H, s), 8,61-8,59(2H, m), 8,22(1H, d, J = 9,0 Hz), 7,97(1H, s), 7,92-7,86(1H, m), 7,80(1H, d, J = 9,0 Hz), 7,69(1H, d, J = 9,0 Hz), 7,59(1H, d, J = 7,8 Hz), 7,40-7,36(1H, m), 7,28 (1H, d, J = 9,0 Hz), 6,48(2H, s l), 5,31(2H, s), 4,94 (1H, m), 4,37 (2H, m), 2,81-2,63(5H, m), 2,44 (1H, m), 2,25(3H, s), 2,14(1H, m), 1,69(1H, m)
VIII-152		10,13(1H, s l), 8,79(1H, s), 8,61-8,58(2H, m), 8,23(1H, dd, J = 1,8 Hz, J = 8,7 Hz), 7,98(1H, d, J = 2,7 Hz), 7,92-7,86(1H, m), 8,80(1H, d, J = 8. 7 Hz), 7. 79(1H, dd, J = 2,7 Hz, J = 9,0 Hz), 7,59(1H, d, J = 7,8 Hz), 7,39- 7,35(1H, m), 7,28(1H,d, J = 9,0 Hz), 5,31(2H, s), 4,91(1H, s l), 4,36-4,24(3H, m), 3,59(1H, m), 2,99-2,812(2H, m), 2,26(3H, s), 2,13(1H, m), 1,50(1H,m).
VIII-153		10,0(1H, l), 8,64(1H, s), 8,62-8,55(2H, m), 8,20(1H, d, J = 8,8), 7,96(1H, s), 7,90-7,87(1H, m), 7,79(1H, d, J = 8,4), 7,68-7,66(1H,m), 7,58(1H, d, J = 8,4), 7,38- 7,35(1H, m), 7,27(1H, d, J = 8,8), 5,30(2H, s), 4,18-4,08(2H, m), 3,43-3,40(1H, m), 3,69(3H, s), 2,84-2,77(2H, m), 2,25(3H, s), 1,88-1,55(3H, m), 1,50-1,38(1H, m).

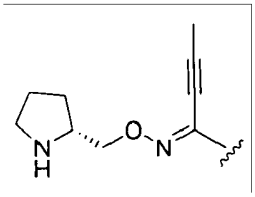
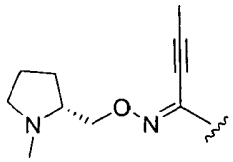
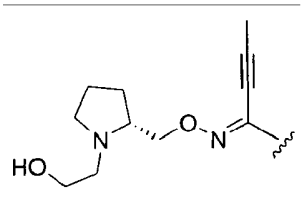
(continuação)

Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-154		10,08(1H, l), 8,75(1H, s), 8,60-8,58(2H, m), 8,21-8,19(1H,m), 7,98-7,97(1H, m), 7,93-7,86(1H, m), 7,79(1H, d, J = 8,8), 7,70-7,67(1H, m), 7,58(1H, d, J = 8,0), 7,38-7,35(1H, m), 7,27(1H, d, J = 9,2), 5,30(2H, s), 4,30-4,20(2H, m), 3,01-2,96(1H, m), 2,68(1H, l), 2,41(3H, s), 2,24(3H, s), 1,99-1,89(1H, m), 1,73-1,66(2H, m), 1,62-1,53(1H, m).
VIII-155		10,0(1H, s l), 8,73(1H, s), 8,60-8,58(2H, m), 8,31(1H, s), 8,22-8,20(1H, m), 7,96(1H, s), 7,90-7,86(1H, m), 7,79(1H, d, J = 8,8), 7,68-7,66(1H, m), 7,59(1H, d, J = 7,6), 7,38-7,35(1H, m), 7,28(1H, d, J = 9,2), 5,30(2H, s), 4,93(1H, s l), 3,02(1H, d, J = 11,6), 2,24(3H, s), 2,06-2,01(1H, m), 1,77-1,70(1H, m).

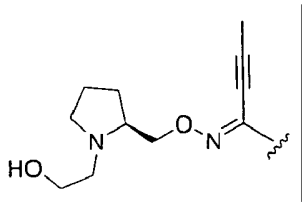
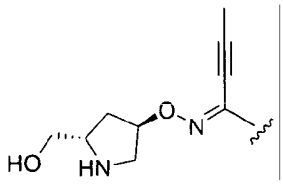
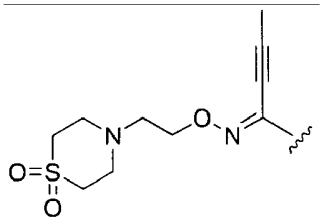
Quadro 36

Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-156		10,13(1H, s l), 8,81(1H, s), 8,61-8,59(2H, m), 8,24(1H, d, J = 10,5 Hz), 7,99(1H, s), 7,92-7,88(1H, m), 7,81(1H, d, J = 9,0 Hz), 7,70(1H, d, J = 9,0 Hz), 7,59(1H, d, J = 7,8 Hz), 7,38-7,36(1H, m), 7,28(1H, d, J = 9,0 Hz), 5,31(2H, s), 4,92(1H, s), 4,28(3H, m), 3,82(1H, m), 3,09(1H, d, 11,4 Hz), 3,83(1H, d, 11,4 Hz), 2,27(3H, s), 1,87(1H, m), 1,65(1H, m)

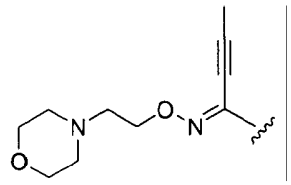
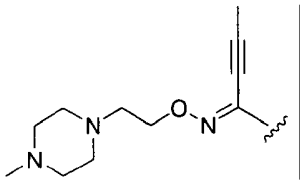
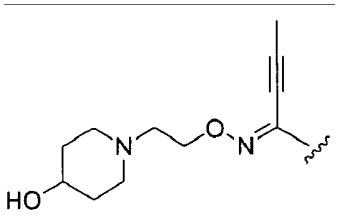
(continuação)

Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-157		10,03(1H, l), 8,73(1H, s), 8,59-8,58(1H, m), 8,55(1H, s), 8,20(1H, d, J = 8,8), 7,94(1H, s), 7,89-7,85(1H, m), 7,78(1H, d, J = 8,4), 7,66-7,64(1H, m), 7,57(1H, d, J = 7,6), 7,38-7,35(1H, m), 7,25(1H, d, J = 8,8), 5,28(2H, s), 4,20-4,08(2H, m), 2,85-2,74(2H, m), 2,24(3H, s), 1,82-1,76(1H m), 1,73-1,58(2H, m), 1,48-1,39(1H, m)
VIII-158		10,07(1H, l), 8,74(1H, s), 8,60-8,58(2H, m), 8,22-8,19(1H,m), 7,98-7,97(1H, m), 7,93-7,86(1H, m), 7,80(1H, d, J = 9,2), 7,70-7,67(1H, m), 7,59(1H, d, J = 7,6), 7,38-7,35(1H, m), 7,28(1H, d, J = 9,2), 5,30(2H, s), 4,30-4,20(2H, m), 3,01-2,96(1H, m), 2,65(1H, l), 2,40(3H, s), 2,24(3H, s), 1,99-1,89 (1H, m), 1,73-1,66(2H, m), 1,62-1,53(1H, m).
VIII-159		10,08(1H, s), 8,73(1H, s), 8,59-8,56(2H, m), 8,21-8,19(1H, m), 7,94(1H, s), 7,90-7,86(1H, m), 7,79(1H, d, J = 8,8), 7,66-7,64(1H, m), 7,58(1H, d, J = 7,6), 7,38-7,35(1H, m), 7,26(1H, d, J = 9,2), 5,29(2H, s), 4,44(1H, s l), 4,25-4,21(1H, m), 4,15-4,11(1H, m), 3,05-2,96(2H, m), 2,46-2,39(1H, m), 2,23(2H, s), 1,92-1,82(1H, m), 1,73-1,63(2H, m), 1,59-1,54(1H, m).

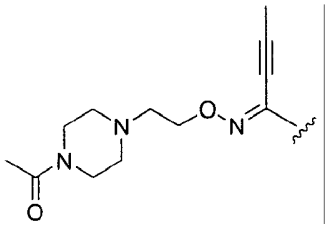
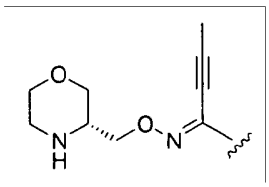
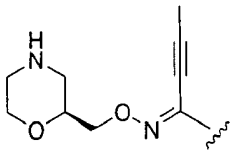
(continuação)

Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-160		10,0(1H, s), 8,72(1H, s), 8,61-8,53(2H, m), 8,21-8,19(1H, m), 7,94(1H, s), 7,89- 7,86(1H, m), 7,79(1H, d, J = 8,8), 7,66-7,64(1H,m), 7,58(1H, d, J = 8,0), 7,38- 7,35(1H, m), 7,26(1H, d, J = 9,2), 5,29(2H, s), 4,44(1H, s l), 4,25-4,21(1H, m), 4,15-4,11(1H, m), 3,05-2,96(2H, m), 2,45-2,39(1H, m), 2,23(3H, s), 1,92-1,82(1H, m), 1,73-1,63(2H, m), 1,60-1,53(2H, m).
VIII-161		10,0(1H. s l), 8,73(1H, s), 8,60-8,57(2H, m), 8,21(1H, d, J = 8,4), 7,95(1H, s); 7,90-7,86(1H, m), 7,79(1H, d, J = 8,8), 7,67-7,65(1H, m), n,58(1H, d, J = 7,6), 7,38-7,35(1H, m), 7,27(1H, d, J = 8,8), 5,30(2H, s), 4,93(1H, s l), 3,02(1H, d, J = 11,6), 2,24(3H, s), 2,06-2,01(1H, m), 1,77-1,70(1H, m)
VIII-162		10,07(1H, s), 8,75(1H, s), 8,61-8,59(2H, m), 8,23(1H, d, J = 8,8 Hz), 7,98(1H, d, J = 2,4 Hz), 7,89(1H, t, J = 8,4 Hz), 7,80(1H, d, J = 8,8 Hz), 7,68(1H, d, J = 6,4 Hz), 7,57(1H, t, J = 11,8 Hz), 7,28(1H, d, J = 8,8 Hz), 5,31(2H, s), 4,40(2H, t J = 5,2 Hz), 3,32(4H, s), 3,09(4H, sl), 2,96(2H, t, J = 5,6 Hz), 2,26(3H, s).

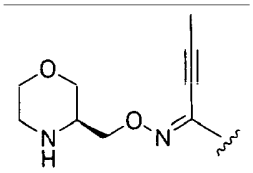
Quadro 37

Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-163		10,07(1H, s), 8,75(1H, s), 8,59(2H, sl), 8,21(1H, d, J = 4,8 Hz), 7,98(1H, s), 7,89(1H, t, J = 7,6 Hz), 7,80(1H, d, J = 8,4 Hz), 7,68(1H, d, J = 8,4 Hz), 7,60(1H, t, J = 8,4 Hz), 7,37(1H, t, J = 7,6 Hz), 7,28(1H, d, J = 8,8 Hz), 5,31(2H, s), 4,40(2H, t, J = 4,8 Hz), 3,60(4H, sl), 2,72(4H, t, J = 4,8 Hz), 2,25(3H, s).
VIII-164		10,0(1H, s), 8,73(1H, s), 8,60-8,57(2H, m), 8,20(1H, d, J = 8,8), 7,96(1H, s), 7,90-7,86(1H, m), 7,79(1H, d, J = 8,4), 7,67-7,65(1H, m), 7,58(1H, d, J = 7,6), 7,38-7,35(1H, m), 7,27(1H, d, J = 8,8), 5,30(2H, s), 4,38-4,35(2H, m), 2,71-2,68(2H, m), 2,31(1H, l), 2,24(3H s), 2,13(3H, s).
VIII-165		10,0(1H, s), 8,73(1H, s), 8,62-8,54(2H, m), 8,21-8,19(1H,m), 7,96(1H, s), 7,90-7,86(1H, m), 7,80-7,78(1H, m), 7,68-7,66(1H, m), 7,59(1H, d, J = 8,0), 7,38-7,36(1H, m), 7,27(1H, d, J = 8,8), 5,30(2H, s), 4,54(1H, s l), 4,37-4,34(2H, m), 2,83-2,75(2H, m), 2,69-2,66(2H, m), 2,24(3H, s), 2,17-2,11 (2H, m), 1,71-1,69(2H, m), 1,71-1,69(2H, m), 1,44-1,32(2H, m).

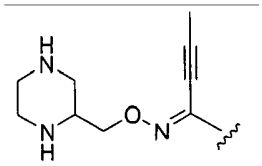
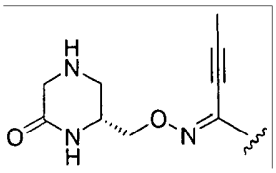
(continuação)

Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-166		10,08(1H, s), 8,75(1H, s), 8,59(2H, sl), 8,22(1H, d, J = 8,8 Hz), 7,80(1H, s), 7,89(1H, t, J = 6,4 Hz) 7,80(1H, d, J = 8,4 Hz), 7,70-7,67(1H, m), 7,59(1H, d, J = 8,4 Hz), 7,37(1H, sl), 7,28(1H, d, J = 8,0 Hz), 5,31(2H, s), 4,41(2H, t J = 4,4 Hz), 3,43(2H, sl), 2,76(2H, sl), 2,26(3H, s), 1,99(3H, s).
VIII-167		10,10(1H, s), 8,73(1H, s), 8,60-8,56(2H, m), 8,20(1H, d, J = 8,8), 7,94(1H, s), 7,90-7,86(1H, m), 7,79(1H, d, J = 8,8), 7,68-7,64(1H,m), 7,58(1H, d, J = 7,6), 7,38-7,35(1H, m), 7,27(1H, d, J = 9,2), 5,29(2H, s), 4,20-4,08(2H, m), 7,79(1H, d, J = 11,2), 3,25-3,20(1H, m), 3,09(1H, l), 2,83-2,70(2H, m), 2,25(3H, s)
VIII-168		10,0(1H. s), 8,73(1H, s), 8,59-8,57(2H, m), 8,19(1H, d, J = 8,8), 7,95(1H, s); 7,89-7,85(1H, m), 7,78(1H, d, J = 8,8), 7,68-7,65(1H, m), 7,58(1H, d, J = 7,6), 7,37-7,34(1H, m), 7,26(1H, d, J = 8,8), 5,29(2H, s), 4,26-4,14(2H, m), 3,75-3,72(2H, m), 2,85(1H, d, J = 12,4), 2,69-2,61(2H, m), 2,45(1H, d, J = 10,8), 2,25(3H, s).

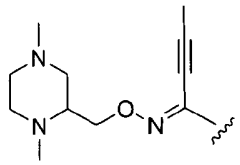
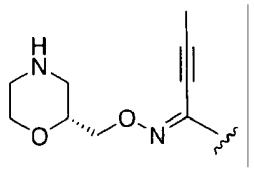
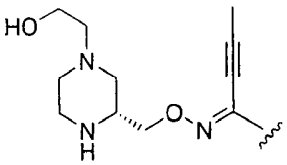
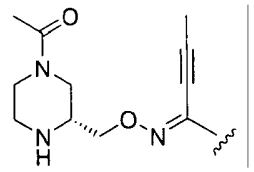
(continuação)

Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-169		10,0(1H, s), 8,74(1H, s), 8,60-8,58(2H, m), 8,20(1H, d, J = 8,8), 7,96(1H, s), 7,90-7,86(1H, m), 7,80(1H, d, J = 8,8), 7,68-7,66(1H, m), 7,59(1H, d, J = 7,6), 7,38-7,35(1H, m), 7,27(1H, d, J = 9,2), 5,30(2H, s), 4,20-4,08(2H, m), 3,79(1H, d, J = 10,4), 3,65(1H, d, J = 11,2), 3,25-3,20(1H, m), 3,09(1H, l),2,83-2,70(2H, m), 2,26(2H, s).

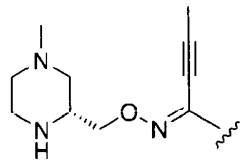
Quadro 38

Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-170		10,09(1H, s l), 8,74(1H, s), 8,61-8,58(2H, m), 8,22(1H, d, J = 10,5 Hz), 7,97(1H, s), 7,92-7,86(1H, m), 7,80(1H, d, J = 9,0 Hz), 7,68(1H, d, J = 10,5 Hz), 7,59(1H, d, J = 8,1 Hz), 7,39-7,35(1H, m), 7,28(1H, d, J = 9,0 Hz), 5,31(2H, s), 4,12(2H, d, 4,5 Hz), 2,95-2,53(5H, m), 2,34-2,09(5H, m)
VIII-171		10,08(1H, s l), 8,74(1H, s), 8,61-8,59(2H, m), 8,21(1H, d, J = 9,0 Hz), 7,98(1H, s), 7,92-7,86(1H, m), 7,81(1H, d, J = 9,0 Hz), 7,75(1H, s), 7,67(1H, d, J = 9,0 Hz), 7,59(1H, d, J = 7,8 Hz), 7,40-7,36(1H, m), 7,29(1H, d, J = 9,0 Hz), 5,31(2H, s), 4,31(2H, m), 3,66(1H, m), 3,27-3,10(2H, m), 2,99-2,80(2H, m)

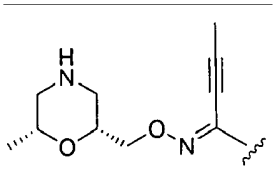
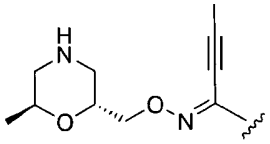
(continuação)

Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-172		10,09(1H, s l), 8,74(1H, s), 8,61-8,59(2H, m), 8,22(1H, d, J = 9,0 Hz), 7,97(1H, s), 7,92-7,86(1H, m), 7,81(1H, d, J = 9,0 Hz), 7,68(1H, d, J = 9,0 Hz), 7,59(1H, d, J = 7,8 Hz), 7,40-7,36(1H, m), 7,29(1H, d, J = 9,0 Hz), 5,31(2H, s), 4,44(1H, m), 4,16(1H, m), 2,70-2,51(4H, m), 2,30-2,16(10H, m), 2,09-1,88(2H, m)
VIII-173		10,0(1H, l), 8,74(1H, s), 8,60-8,58(2H, m), 8,20(1H, d, J = 8,8), 7,97(1H, s), 7,90-7,86(1H, m), 7,80(1H, d, J = 8,4), 7,68-7,66(1H,m), 7,59(1H, d, J = 8,0), 7,38-7,35(1H, m), 7,28(1H, d, J = 9,2), 5,30(2H, s), 4,26-4,14(2H, m), 3,75-3,72(2H, m), 3,48-3,42(2H, m), 2,85(1H, d, J = 12,4), 2,69-2,60(2H, m), 2,45(1H, d, J = 10,4); 2,26(3H, s)
VIII-174		(sal de tri-HCl) 12,31(1H, s l), 9,41(1H, s), 8,97(1H, s), 8,73(1H, d, J = 1,8 Hz), 8,49(1H, d, 8,7 Hz), 8,17-8,05(2H, m), 7,94(1H, s), 7,77(1H, d, J = 7,5 Hz), 7,69(1H, d, 8,7 Hz), 7,59(1H t, J = 5,7 Hz), 7,38(1H, d, J = 8,7 Hz), 5,46(2H, s), 4,60(2H, m), 4,35-3,31(12H, m), 2,30(3H, s).
VIII-175		

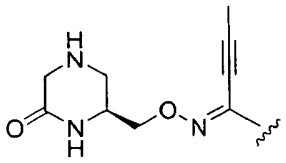
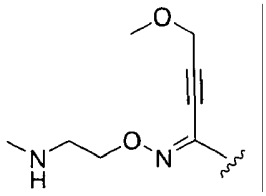
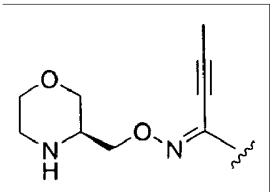
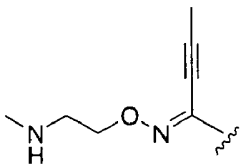
(continuação)

Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-176		(sal de tri-HCl) 12,31(1H, s l), 9,41(1H, s), 8,97(1H, s), 8,73(1H, d, J = 5,4 Hz), 8,49(1H, d, J = 8,7 Hz), 8,13(1H, s), 8,07(1H, d, J = 9,0 Hz), 7,94(1H, s), 7,72(1H, d, J = 8,7 Hz), 7,02(1H, d, J = 9,0 Hz), 7,59(1H, s), 7,38(1H, d, J = 9,0 Hz), 5,46(2H, s), 4,65-3,62(10H, m), 2,89(3H, s), 2,30(3H,s).

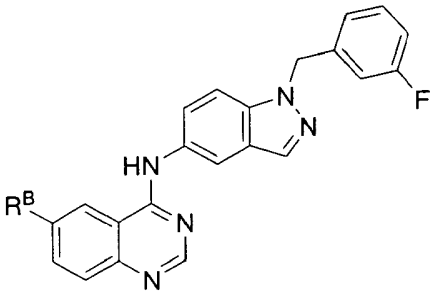
Quadro 39

Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-177		10,1(1H, s), 8,74(1H, s), 8,59(2H, s l), 8,21(1H, d, J = 8,8 Hz), 7,97(1H, s), 7,85-7,92(1H, m), 7,80(1H, d, J = 8,4 Hz), 7,67(1H, d, J = 9,6 Hz), 7,59(1H, d, J = 6,4 Hz), 7,34-7,40(1H, m), 7,29(1H, d, J = 8,8 Hz), 5,31(2H, m), 4,10-4,35(2H, m), 3,75-3,82(1H, m), 3,48(1H, m), 2,85(1H, d, J = 12 Hz), 2,74(1H, d, J = 13 Hz), 2,34-2,41(1H, m), 2,26(4H, s l), 1,03(3H, d, J = 6,0 Hz)
VIII-178		10,1(1H, s), 8,74(1H, s), 8,59(2H, s l), 8,21(1H, d, J = 8,8 Hz), 7,97 (1H, s), 7,79-7,93(2H, m), 7,66-7,70(1H, m), 7,59(1H, d, J = 6,4 Hz), 7,38(1H, s l), 7,29(1H, d, J = 8,8 Hz), 5,31(2H, m), 4,37-4,56(2H, m), 3,95-4,02(1H, m), 3,80-3,88(1H, m), 2,62-2,85(3H, m), 2,31-2,4(1H, m), 2,26(3H, s), 1,06(3H, d, J = 5,2 Hz)

(continuação)

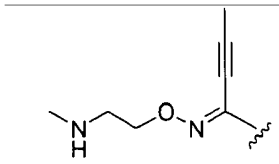
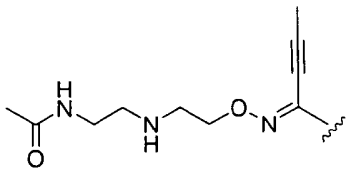
Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-179		10,06(1H, s l), 8,75(1H, s), 8,61-8,59(2H, m), 8,22(1H, d, J = 9,0 Hz), 7,97(1H, s), 7,92-7,86(1H, m), 7,81(1H, d, J = 9,0 Hz), 7,76(1H, s), 7,69(1H, d, J = 9,0 Hz), 7,59(1H, d, J = 7,8 Hz), 7,40-7,36(1H, m), 7,29(1H, d, J = 9,0 Hz), 5,31(2H, s), 4,30 (2H, m), 3,65(1H, m), 3,16(2H, m), 2,99-2,80(2H, m), 2,26(3H, s)
VIII-180		10,0(1H, s l), 8,76(1H, s), 8,60-8,58(2H, m), 8,19(1H, d, J = 8,8), 7,97(1H, s), 7,89-7,86(1H,m), 7,81(1H, d, J = 8,8), 7,68-7,66(1H, m), 7,58(1H, d, J = 7,6), 7,38-7,35(1H, m), 7,27(1H, d, J = 8,8), 5,30(2H, s), 4,51(2H, s), 4,38-4,35(2H, m), 3,40(3H, s), 2,87-2,84(2H, m), 2,34(3H, s)
VIII-181		10,0(1H, s), 8,76(1H, s), 8,59(2H, s), 8,19(1H, d, J = 8,8), 7,97(1H, s), 7,90-7,86(1H, m), 7,82(1H, d, J = 8,8), 7,69-7,66(1H, m), 7,59 (1H, d, J = 8,0), 7,38-7,35(1H, m), 7,28(1H, d, J = 8,8), 5,30(2H, s), 4,52(2H, s), 4,25-4,15(2H, m), 3,82-3,79(1H, m), 3,67-3,64(1H, m), 3,40(3H, s), 3,26-3,21(2H, m), 3,14-3,05(1H, m), 2,81-2,72(2H, m)
VIII-182		10,1(1H, s), 8,79(1H, s), 8,60(2H, s), 8,25(1H, d, J = 7,6 Hz), 7,98(1H, s), 7,89(1H, sl), 7,81(1H, d, J = 7,6 Hz), 7,69(1H, d, J = 7,6 Hz), 7,60(1H, d, J = 7,2 Hz), 7,38(1H, sl), 7,29(1H, d, J = 8,4 Hz), 5,31(2H, s), 4,43(2H, sl), 3,14(2H, sl), 2,52(3H, s), 2,27(3H, s)

Fórmula química 83

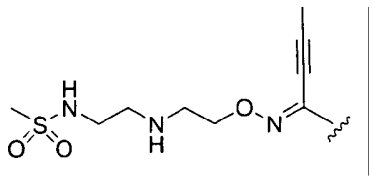
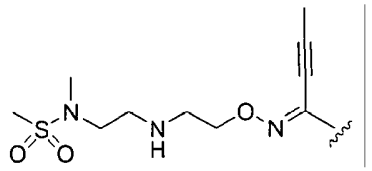
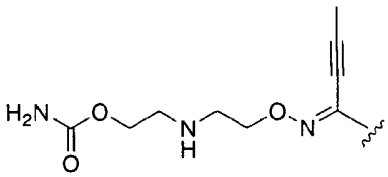
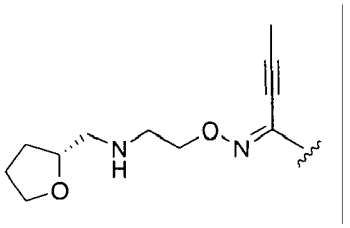


(VIII)

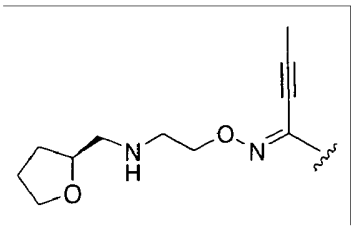
Quadro 40

Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-183		10,19(1H, s), 8,78(1H, s), 8,53(1H, s), 8,23(1H, dd, J = 8,4 Hz, J = 4,0 Hz), 8,17(1H, s), 8,14(1H, s), 7,80-7,65(3H, m), 7,40-7,35(1H, m), 7,13-7,04(3H, m), 5,72(2H, s), 4,32(2H, t, J = 6,0 Hz), 2,86(2H, t, J = 6,0 Hz), 2,35(3H, s), 2,25(3H, s).
VIII-184		(sal de di-HCl) 12,46(1H, s), 9,37(1H, s), 8,87(1H, s), 8,48(1H, d, J = 8,7 Hz), 8,27(1H, t, J = 5,4 Hz), 8,24(1H, s), 8,03(2H, m), 7,85(1H, d, J = 9,0 Hz), 7,68(1H, d, 9,0 Hz), 7,35(1H, s), 7,13- 7,05(3H, m), 5,75(2H, s), 4,58(2H, m), 7,13- 7,05(3H, m), 5,75(2H, s), 4,58(2H, m), 3,51-3,37(4H, m), 3,11(2H, m), 2,27(3H, s), 1,01(1H, s).

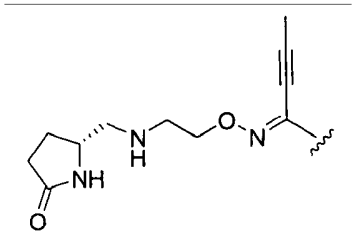
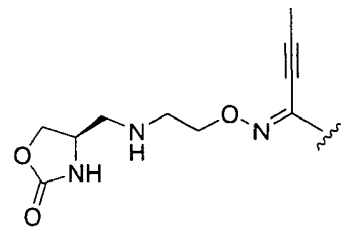
(continuação)

Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-185		(sal de di-HCl) 10,12(1Hs), 8,82(1H, d, J = 1,5 Hz), 8,52(1H, s), 8,22(1H, dd, J = 1,8 Hz, J = 8,7 Hz), 8,14(1H, s), 7,80(1H, s), 7,80(1H, s), 7,77-7,68(3H, m), 7,40-7,33(1H, m), 7,12-7,04(3H, m), 5,71(2H, s), 4,86(1H, s l), 4,28(3H, m), 3,58(1H, m), 2,95-2,78(2H, m), 2,25(3H, s), 2,11(1H, m), 1,47(1H, m).
VIII-186		10,18(1H, s), 8,78(1H, s), 8,52(1H, s), 8,23-8,12(3H, m), 7,79-7,65(3H, m), 7,41-7,32(1H, m), 7,18(7,02)(3H, m), 5,71 (2H, s), 4,31(2H, m), 3,14(2H, m), 2,29(2H, m), 2,87(3H, s)2,77(6H, m), 2,24(3H, s).
VIII-187		10,19(1Hs); 8,78(1H, s), 8,52(1H, s), 8,23-8,12(3H, m), 7,80-7,65(3H, m), 7,38-7,33(1H, m), 713-7,03(3H, m), 6,49(2H, s l), 5,71(2H, s), 4,31(2H, m), 4,04-3,95(2H, m), 2,92(2H, m), 2,78(2H, m), 2,25(3H, s).
VIII-188		(sal de di-HCl) 12,09(1H, s), 8,96(1H, s), 8,83 (1H, s), 8,43(1H, d, J = 8,7 Hz), 8,06(1H, s), 7,97(1H, d, J = 8,4 Hz), 7,83(1H, d, J = 9,0 Hz), 7,67(1H, d, J = 1,8 Hz), 7,65(1H, dd, J = 2,1 Hz, J = 9,0 Hz), 7,41-7,34(1H, m), 7,14-7,05(3H, m), 5,71(2H, s), 4,54(2H, m), 4,19(1H, m), 3,83-3,70(2H, m), 3,68-2,95(5H, m), 2,27(3H, s), 2,04(1H, m), 1,93(1H, m), 1,56(1H, m).

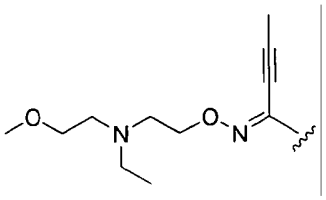
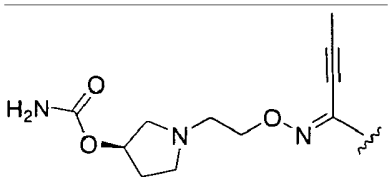
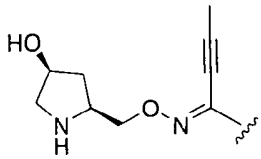
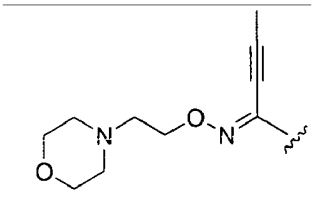
(continuação)

Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-189		(sal de di-HCl) 12,21(1H, s l), 8,97(1H, s l), 8,84(1H, s), 8,43(1H, dd, J = 1,5 Hz, J = 9,0 Hz), 8,0 7(1H, s), 8,01(1H, s), 7,99(1H. d, J = 9,0 Hz), 7,84(1H, d, J = 9,0 Hz), 7,67(1H, dd, J = 1,8 Hz, J = 9,0 Hz), 7,41-7,32(1H, m), 7,14- 7,05(3H, m), 5,74(2H, s), 4,59(2H, m), 4,21(1H, m), 3,82-3,65(2H, m), 3,62-3,05(8H, m), 2,28(3H, s), 2,02(1H, m), 1,83(1H, M), 1,55(1H, m).

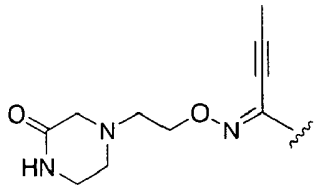
Quadro 41

Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-190		(sal de di-HCl) 12,18(1H, s), 9,29(1H, s), 8,45(1H, dd, J = 1,2, J = 9,0 Hz), 8,23(1H, s), 8,06(1H, s), 8,06(1H, d, J = 1,2 Hz), 7,99(1H, d, J = 8,7 Hz), 7,87-7,82(1H, m), 7,67(1H, dd, J = 1,2 Hz, J = 9,0 Hz), 7,39-7,14(1H, m), 7,14-7,05(3H, m), 5,74(2H, s), 4,61(2H(, m), 3,95(1H, m), 8,23(2H, m), 3,13(3H, m), 2,28(3H, s), 2,17(1H, m), 1,78(1H, m).
VIII-191		(sal de di-HCl) 12,18(1H, s), 9,12(1H, s), 8,87(1H, s), 8,46(1H, d, J = 8,7 Hz), 8,43(1H, s), 8,23(1H, s), 8,04-7,97(2H, m), 7,87-7,82(1H, m), 7,64(1H, dd, J = 1,2 Hz, J = 9,0 Hz), 7,37-7,14(1H, m), 7,11-7,05(3H, m), 5,74(2H, s), 4,61(2H(, m), 4,09-3,26(7H, m), 2,26(3H, s), 2,17(1H, m), 1,79(1H, s).

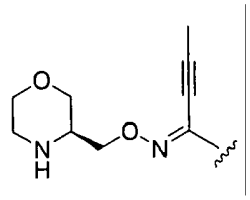
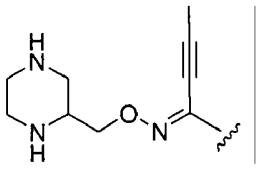
(continuação)

Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-192		10,17(1H, s), 8,78(1H, s), 8,51(1H,s), 8,20(1H, dd, J = 1,8 Hz, J = 8,7 Hz), 8,14(1H, s), 7,80-7,65(3H, m), 7,40-7,33(1H, m), 7,13-7,03(3H, m), 5,71(2H, s), 4,31(2H, t, J = 5,7 Hz), 3,41(2H, t, J = 6,3 Hz), 3,22(3H, s), 2,85(2H, m), 2,70-2,57(4H, m), 2,23(3H, s), 0,99(2H, t, J = 7,2 Hz).
VIII-193		10,19(1H, s), 8,78(1H, s), 8,52(1H, s), 8,21(1H, d, J = 8,4 Hz), 8,16(1H, s), 8,13(1H, s), 7,78- 7,65(3H, m), 7,49-7,33(1H, m), 7,13-7,04(3H, m), 6,48(2H,s l), 5,71(2H, s), 4,93(1H, m), 4,36(2H, t, J = 5,7 Hz), 2,80(3H, m), 2,71(2H, m), 2,42(1H, m), 2,24(3H, s), 2,10(1h, m), 1,66(1H, m).
VIII-194		10,21(1H, s), 8.,82(1H, d, J = 1,5 Hz), 8,52(1H, s), 8,22(1H, dd, J = 1,8 Hz, J = 8,7 Hz), 8,14(1H, s), 7,80(1H, s), 7,77-7,66(3H, m), 7,40- 7,33(1H, m), 7,12-7,04(3H, m), 5,71(2H, s), 4,86(1H,s l), 4,28(3H, m), 3,58(1H, m), 2,95-2. 78(2H, m), 2,25(3H, s), 2,11(1H, m), 1,47(1H, m).
VIII-195		10,17(1H, s), 8,78(1H, d, J = 1,8 Hz), 8,52(1H, s), 8,19(1H, dd, J = 1,8 Hz, J = 10,5 Hz), 8,13(1H, s), 7,80(1H, s), 7,77-7,33(1H, m), 7,12-7,03(3H, m), 5,71(2H, s), 439(2H, t, J = 5,7 Hz), 3,58(4H, t, J = 4,8 Hz), 2,71(2H, t, J = 6,0 Hz), , 2,50(2H, m), 2,24(3H, s).

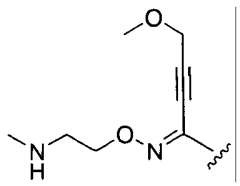
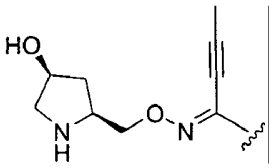
(continuação)

Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-196		10,19(1H, s), 8,78(1H, d, J = 1,5 Hz), 8,19(1H, dd, J = 1,8 Hz, J = 10,5 Hz), 8,16(1H, s), 8,13(1H, d, J = 1,5 Hz), 7,80(1H, s), 7,80- 7,66(4H, m), 7,40-7,33(1H, m), 7,13-7,06(3H, m), 5,71(2H, s), 4,41(2H, t, J = 5,2 Hz), 3,16(2H, m), 3,10(2H, s), 2,80(1H, t, J = 5,7 Hz), 2,67(3H, s), 2,25(3H, s).

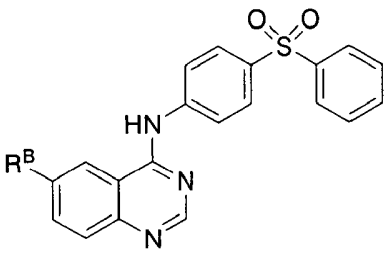
Quadro 42

Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-197		10,21(1H, s), 8,79(1H, d, J = 1,8 Hz), 8,53(1H, s), 8,21(1H, dd, J = 1,8 Hz, J = 8,7 Hz), 8,17(1H, s), 8,13(1H, d, J = 1,5 Hz), 7,79(1H, d, J = 13,2 Hz), 7,76(1H, d, J = 13,2 Hz), 7,67(1H, dd, J = 1,8 Hz, J = 9,0 Hz), 7,41-7,34(1H, m), 7,16-7,04(3H, m), 5,72(2H, s), 4,20-4,09(2H, m), 3,79(1H, dd, J = 2,7 Hz, J = 10,8 Hz), 3,68-3,64(1H, m), 3,30-3,19(1H, m), 3,13-3,10(1H, m), 2,78-2,74(3H, m), 2,26(3H, s).
VIII-198		10,20(1H, s l), 8,79(1H, s), 8,53(1H, s), 8,22-8,13(3H, m), 7,81-7,66(3H, m), 7,41-7,33(1H, m) 7,13-7,04(3H, m), 5,72(2H, s), 4,13(2H, d, J = 5,2 Hz), 3,00-2,51(6H, m), 2,39-2,26(4H, m)

(continuação)

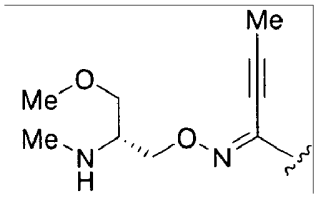
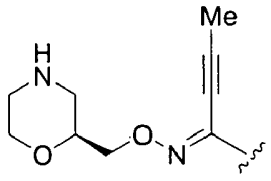
Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-199		(sal de di-HCl) 12,69(1Hs l), 9,44(1H, s), 8,69(1H, s), 8,47(1H, d, J = 8,1 Hz), 8,23(1H, d, J = 2,1 Hz), 7,38(1H, s), 7,19-7,01(1H, m), 5,74(2H, s), 4,64(5H, m), 4,01(1H, m), 3,39-3,21(4H, m), 2,59(3H, s).
VIII-200		10,19(1H, s), 8,81(1H, s), 8,53(1H, s), 8,21-8,14(3H, m), 7,82(7,82-7,65(3H, m), 7,41(1H, m), 7,15-7,04(13H, m), 5,71(2H, s), 4,68(1H, s l), 4,51(2H, s), 4,27(2H, m), 4,18(1H, m), 3,42(2H, m), 3,45(3H, s), 2,87(1H, m), 2,69(1H, m), 2,04(1H, m), 1,41(1H, m).

Fórmula química 84

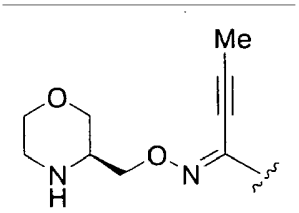
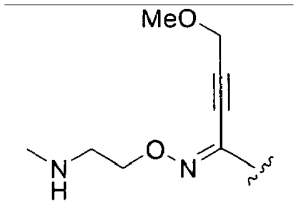
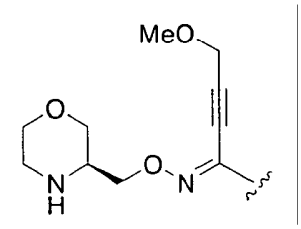


(VIII)

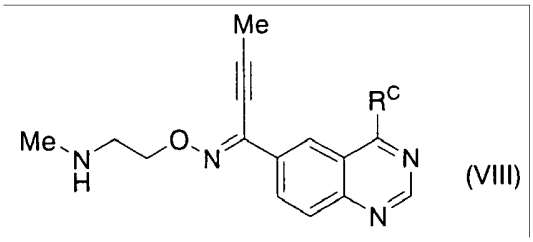
Quadro 43

Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-205		10,43-10,40(1H, m), 8,79(1H, s), 8,70(1H, s), 8,25(1H, d, J = 8,4 Hz), 8,11(2H, sl), 7,98-7,96(4H, m), 7,85 (1H, d, J = 7,2 Hz), 7,69-7,62(3H, m), 4,24-4,20(2H, m), 3,28(3H, s), 2,94(1H, t, J = 6,4 Hz), 2,38(3H, s), 2,25 (3H, s).
VIII-206		10,44(1H, sl), 8,78(1H, d, J = 1,5 Hz), 8,67(1H, sl), 8,24(1H, d, J = 9,0 Hz), 8,16-8,05(2H, m), 7,99-7,94(4H, m), 7,84(1H, d, J = 8,7 Hz), 7,71-7,60(3H, m), 4,24(1H, dd, J = 6,3 Hz, J = 11,7 Hz), 4,16(1H, dd, J = 4,8 Hz, J = 11,7 Hz), 3,75-3,71(2H, m), 3,51-3,37(1H, m), 2,84(1H, dd, J = 2,4 Hz, J = 12,3 Hz), 2,73-2,58(2H, m), 2,50-2,42(1H, m), 2,25(3H, s).

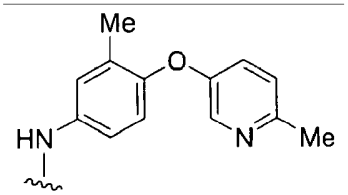
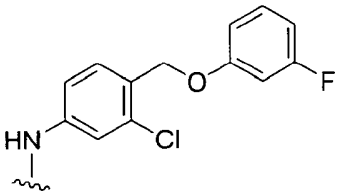
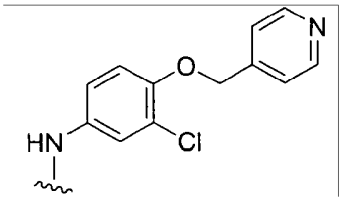
(continuação)

Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-207		10,45(1H, sl), 8,78(1H, d, J = 1,5 Hz), 8,67(1H, sl), 8,24(1H, dd, J = 1,5 Hz, J = 8,7 Hz), 8,12-8,09(2H, m), 7,99-7,95(4H, m), 7,85(1H, d, J = 8,7 Hz), 7,71-7,61(3H, m), 4,18(1H, dd, J = 6,0 Hz, J = 11,1 Hz), 4,12(1H, dd, J = 6,3 Hz, J = 11,1 Hz), 3,78(1H, dd, J = 2,7 Hz, J = 10,5 Hz), 3,65(1H, dt, J = 11,1 Hz, J = 2,7 Hz), 3,11-3,07(1H, m), 2,81-2,69(3H, m), 2,25(3H, s).
VIII-208		10,42(1H, s), 8,84(1H, s), 8,69(1H, s), 8,25(1H, d, J = 8,8 Hz), 8,13(1H, d, J = 8,4 Hz), 8,00-7,97(3H, m), 7,87(1H, d, J = 8,8 Hz), 7,97-7,62(5H, m), 4,51(2H, s), 4,42(2H, t., J = 5,2 Hz), 3,37(3H, s), 2,97(2H, t, J = 4,8 Hz), 2,41(3H, s).
VIII-209		10,45(1H, sl), 8,80(1H, sl), 8,68(1H, sl), 8,23(1H, d, J = 7,5 Hz), 8,14-8,06(2H, m), 7,99-7,95(4H, m), 7,87(1H, d, J = 9,0 Hz), 7,69-7,60(3H, m), 4,52(2H, s), 4,23(1H, dd, J = 6,3 Hz, J = 10,8 Hz), 4,17(1H, dd, J = 6,3 Hz, J = 10,8 Hz), 3,80(1H, dd, J = 2,7 Hz, J = 11,1 Hz), 3,67-3,64(1H, m), 3,40(3H, s), 3,12-3,07(1H, m).

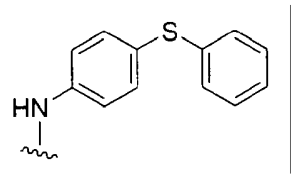
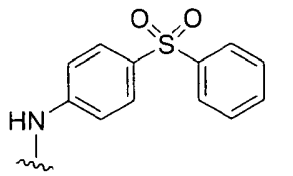
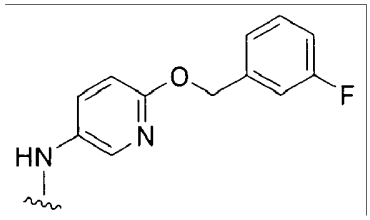
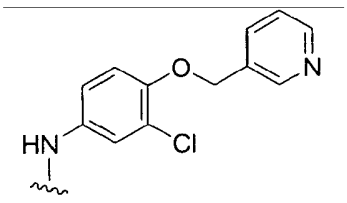
Fórmula química 85



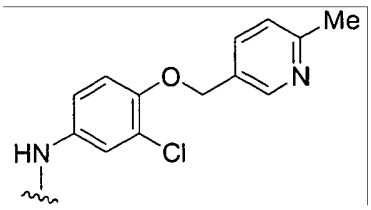
Quadro 44

N° do Composto	R^C	RMN de ^1H (d_6-DMSO)
VIII-210		10,13(1H, s), 8,82(1H, s), 8,60(1H, s), 8,26(1H, d, J = 9,2 Hz), 8,18(1H, s), 7,82(1H, d, J = 8,8 Hz), 7,74(1H, s), 7,64(1H, d, J = 9,2 Hz), 7,27-7,22(2H, m), 6,99(1H, d, J = 8,4 Hz), 4,50(2H, t, J = 5,2 Hz), 2,64(3H, s), 2,50(2H, sl), 2,45(3H, s), 2,28(3H, s), 2,23(3H, s).
VIII-211		10,26(1H, s l), 8,80(1H, s), 8,66(1H, s), 8,26-8,23(1H, m), 8,14(1H, s), 7,88-7,79(2H, m), 7,62(1H, d, J = 8,4), 7,34(1H, dd, J = 8,4, 15,2), 6,95-6,88(2H, m), 6,82-6,78(1H, m), 5,16(2H, s), 4,35(2H, t, J = 6,0 Hz), 2,92(2H, t, J = 6,0 Hz), 2,38(3H, s), 2,26(3H, s), 2,26(3H, s).
VIII-212		10,0(1H, s l), 8,74(1H, s), 8,62-8,58(3H, m), 8,21(1H, d, J = 8,8), 7,97(1H, s), 7,80(1H, d, J = 8,8), 7,69-7,67(1H, m), 7,48-7,47(2H, m), 7,25(1H, d, J = 9,2), 5,32(2H, s), 4,34-4,31(2H, s), 2,89-2,86(2H, m), 2,36(3H, s), 2,25(3H, s).

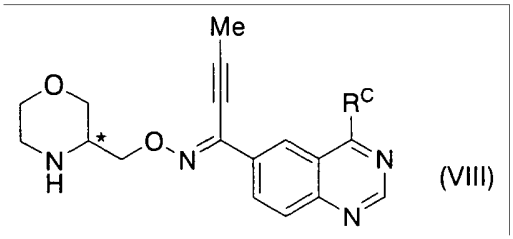
(continuação)

Nº do Composto	R^C	RMN de ^1H (d_6-DMSO)
VIII-213		10,43(1H, s), 9,23(1H, s), 9,21(1H, s), 8,64(1H, s), 8,26(1H, d, J = 6,6 Hz), 7,93(2H, d, J = 3,9 Hz), 7,84(1H, d, J = 6,9 Hz), 7,45(2H, d, J = 5,7 Hz), 7,35(1H, d, J = 5,4 Hz), 7,2 7(2H, t, J = 5,7 Hz), 4,56(2H, d, J = 3,9 Hz), 2,64(3H, s), 2,28(3H, s), 1,99(3H, s).
VIII-214		8,85(1H, s), 8,80(1H, s), 8,26(1H, d, J = 6,6 Hz), 8,12(1H, d, J = 6,3 Hz), 7,99-7,96(4H, m), 7,85(1H, d, J = 6,6 Hz), 7,71-7,62(3H, m), 4,33(2H, t, J = 4,2 Hz), 2,86(2H, t, J = 4,5 Hz), 2,35(3H, s), 2,25(3H, s).
VIII-215		10,15(1H, s), 8,77(1H, s), 8,55(1H, s), 8,47(1H, s), 8,24(1H, d, J = 9,2 Hz), 8,07(1H, d, J = 9,2 Hz), 7,81(1H, d, J = 9,2 Hz), 7,47-7,39(1H, m), 7,32-7,28(2H, m), 7,16(1H, t, J = 7,6 Hz), 7,00(1H, d, J = 8,8 Hz), 5,41(1H, s), 4,41(2H, t, J = 5,6 Hz), 3,10(2H, t, J = 5,2 Hz), 2,49(3H, s), 2,26(3H, s).
VIII-216		10,3(1H, s), 8,84(1H, s), 8,72(1H, s), 8,42-8,65(2H, m), 8,26(1H, d, J = 7,6 Hz), 7,98(1H, s), 7,91(1H, s l), 7,81(1H, s l), 7,71(1H, s l), 7,47(1H, s l), 7,34(1H, d, J = 8,0 Hz), 5,30(2H, s), 4,53(2H, s l), 3,38(2H, s l), 2,68(3H, s), 2,26(3H, s).

Quadro 45

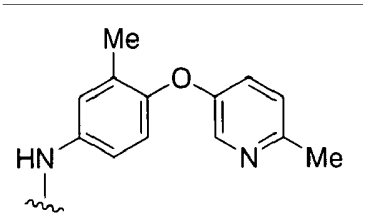
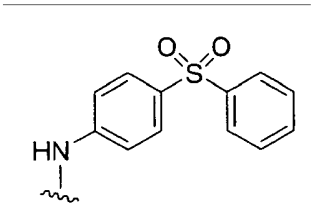
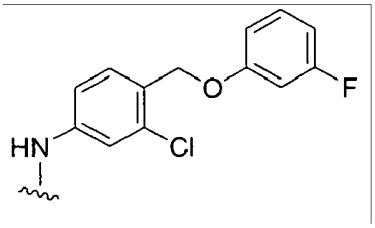
Nº do Composto	R^C	RMN de ^1H (d_6-DMSO)
VIII-217		10,1(1H, s), 8,76(1H, s), 8,59(1H, s), 8,57(1H, s), 8,24(1H, d, J = 10 Hz), 7,94(1H, sl), 7,67-7,73(3H, m), 7,29-7,35(2H, m), 5,24(2H, s), 4,40(2H, t, J = 5,6 Hz), 3,06(2H, t, J = 5,2 Hz), 2,49(3H, s), 2,48(3H, s), 2,26(3H, s)

Fórmula química 86

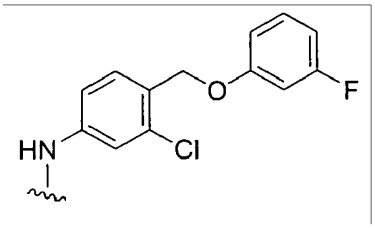


(em que um átomo marcado com * é um átomo de carbono assimétrico)

Quadro 46

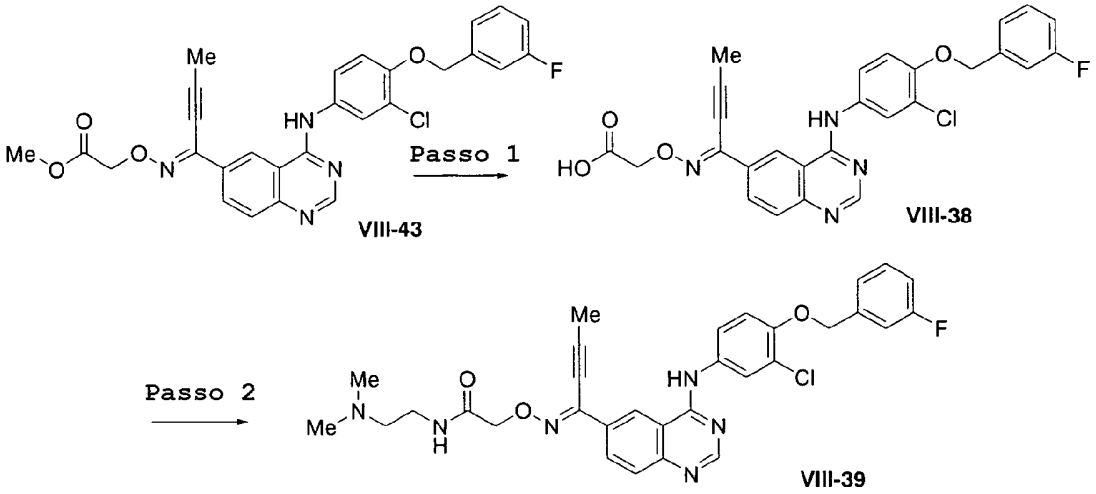
Nº do Composto	*	R^C	RMN de ^1H (d_6-DMSO)
VIII-218	S		(sal de tri-HCl) 12,18(1H, sl), 9,78(1H, m), 9,61(1H, m), 9,36(1H, s), 8,94(1H, s), 8,48(1H, dd, J = 1,8 Hz, J = 9,0 Hz), 8,41(1H, d, J = 3 Hz), 8,03(1H, d, J = 9 Hz), 7,76-7,73(2H, m), 7,64-7,60(2H, m), 7,13(1H, d, J = 8,7 Hz), 4,51-4,49(2H, m), 2,60(3H, s), 2,29(3H, s), 2,27(3H, s).
VIII-219	R		10,46(1H, sl), 8,78(1H, d, J = 1,5 Hz), 8,67(1H, s), 8,24(1H, dd, J = 1,5 Hz, J = 8,7 Hz), 8,12-8,09(2H, m), 7,99-7,95(4H, m), 7,85(1H, d, J = 8,7 Hz), 7,71-7,60(3H, m), 4,17(1H, dd, J = 5,7 Hz, J = 11,1 Hz), 4,12(1H, dd, J = 6,3 Hz, J = 11,1 Hz), 3,78(1H, dd, J = 2,7 Hz, J = 10,5 Hz), 3,65(1H, dt, J = 10,8 Hz, J = 2,7 Hz), 3,26-3,18(1H, m), 3,13-3,05(1H, m), 2,82-2,70(2H, m), 2,25(3H, s).
VIII-220	S		10,26(1H, sl), 8,79(1H, s), 8,67(1H, s), 8,23(1H, d, J = 8,8 Hz), 8,14(1H, s), 7,84(1H, d, J = 8,8 Hz), 7,62(1H, d, J = 8,8 Hz), 7,35(1H, dd, J = 8,0, J = 15,6), 6,96-6,86(2H, m), 6,82-6,78(1H, m), 5,16(2H, s), 4,20-4,11(2H, m), 3,79(1H, d, J = 10,8 Hz), 3,66(1H, d, J = 11,2 Hz), 3,22(2H, t, d= 10,4), 3,10-3,02(1H, m), 2,81-2,68(2H, m), 2,26(3H, s).

(continuação)

Nº do Composto	*	R^C	RMN de ^1H (d_6-DMSO)
VIII-221	R		10,26(1H, sl), 8,79(1H, s), 8,67(1H, s), 8,23(1H, d, J = 9,6 Hz), 8,14(1H, s), 7,85-7,83(1H, m), 7,62(1H, d, J = 8,8 Hz), 7,35(1H, dd, J = 8,0, J = 15,6), 6,95-6,88(2H, m), 6,82-6,78(1H, m), 5,16(2H, s), 4,20-4,11(2H, m), 3,79(1H, d, J = 10,8 Hz), 3,66(1H, d, J = 11,2 Hz), 3,22(2H, t, d= 10,4), 3,10-3,02(1H, m), 2,81-2,68(2H, m), 2,26(3H, s)

Exemplo 11

Fórmula química 87



Passo 1 Síntese de 4-(3-cloro-4-(3-fluorobenziloxi)fenilamino)-6-(carboximetoxiimino)-2-butin-1-il)quinazolina (VIII-38)

4-(3-Cloro-4-(3-fluorobenziloxi)fenilamino)-6-(metoxicarbonilmetoxiimino)-2-butin-1-il)quinazolina (VIII-43, 1,2 g) foi dissolvida numa mistura de 12 mL de tetra-hidrofurano e 12 mL de metanol, e foram adicionados 1,5 mL de solução aquosa de hidróxido de sódio a 2 mol/L, seguido de agitação à temperatura ambiente durante 1,5 horas. A mistura reaccional foi diluída com 20 mL de acetato de etilo, foram adicionados 1,6 mL de ácido clorídrico 2 mol/L e foi adicionada água, desse modo, foi precipitada uma substância alvo. Foi recolhido um precipitado por filtração, lavado com água e acetato de etilo, e seco para obter 4-(3-cloro-4-(3-fluorobenziloxi)fenilamino)-6-(carboximetoxiimino)-2-butin-1-il)quinazolina (VIII-38, 0,9 g) como um sólido amarelo.

RMN de ^{1}H (d_6-DMSO, δ): 10,18 (1H, s l), 8,77 (1H, s), 8,60 (1H, s), 8,19 (1H, dd, J = 2,0, 11,6 Hz), 7,95 (1H, d, J = 3,2 Hz), 7,80 (1H, d, J = 11,6 Hz), 7,67 (1H, dd, J = 3,2, 11,6 Hz), 7,51-7,44 (1H, m), 7,35-7,26 (3H, m), 7,22-7,15 (1H, m), 5,27 (2H, s), 4,83 (2H, s), 2,27 (3H, s).

Passo 2 Síntese de 4-(3-cloro-4-(3-fluorobenziloxi)fenilamino)-6-((2-dimetilaminoetil-carbamoil)metoxiimino)-2-butin-1-il)quinazolina (VIII-39)

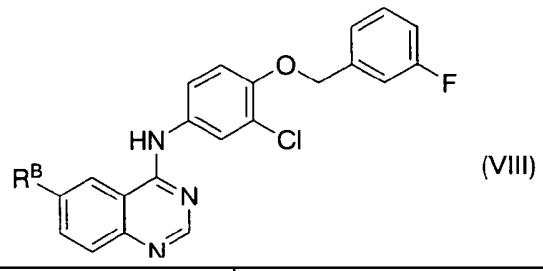
4-(3-Cloro-4-(3-fluorobenziloxi)fenilamino)-6-(carboximetoxiimino)-2-butin-1-il)quinazolina (VIII-38, 70 mg), 24 mg de 1-hidroxibenzotriazole e 27 mg de cloridrato de 1-etil-

3-(3-dimetilaminopropil)carbodiimida foram dissolvidos em 1,4 mL de N,N-dimetilformamida, esta foi agitada à temperatura ambiente durante 5 minutos e foram adicionados 22 µL de N,N-dimetiletilenodiamina, seguido de agitação à temperatura ambiente durante 2 horas. Depois de a reacção estar completa, a mistura reaccional foi diluída com acetato de etilo, e foram adicionadas água e solução aquosa saturada de bicarbonato de sódio para as separar camadas. A camada orgânica foi lavada com água e seca sobre sulfato de sódio, e o filtrado foi concentrado. Foi adicionado acetato de etilo ao resíduo concentrado para solidificar o material e o sólido foi recolhido por filtração, e seco para obter 4-(3-cloro-4-(3-fluorobenziloxi)fenilamino)-6-((2-dimetilaminoetil-carbamoil)metoxiimino)-2-butin-1-il)quinazolina (VIII-39, 30 mg) como um cristal incolor.

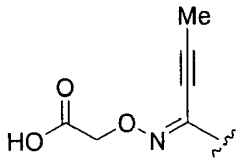
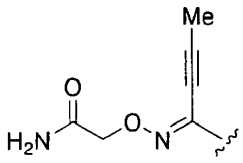
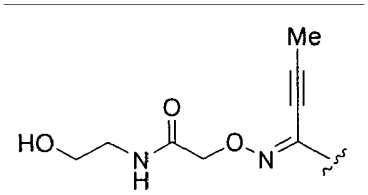
RMN de ^{1}H (d_6-DMSO, δ): 10,12 (1H, s), 8,77 (1H, s), 8,59 (1H, s), 8,19 (1H, dd, J = 2,0, 12,0 Hz), 8,08 (1H, s l), 7,95 (1H, d, J = 3,2 Hz), 7,80 (1H, d, J = 11,6 Hz), 7,70-7,62 (2H, m), 7,51-7,44 (1H, m), 7,34-7,26 (3H, m), 7,21-7,15 (1H, s), 5,27 (2H, s), 4,69 (2H, s), 3,22 (2H, dd, J = 8,4, 16,0 Hz) 2,31 (1H, t, J = 8,4 Hz), 2,28 (3H, s), 2,11 (6H, s).

De acordo com o mesmo modo que o do Exemplo 11 foi sintetizado o composto seguinte.

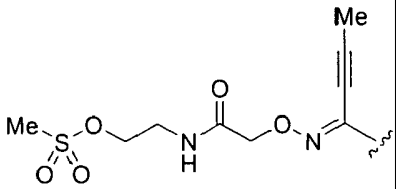
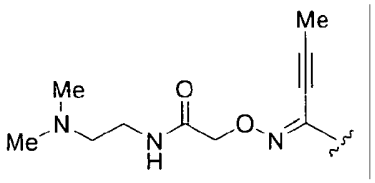
Quadro 47



(VIII)

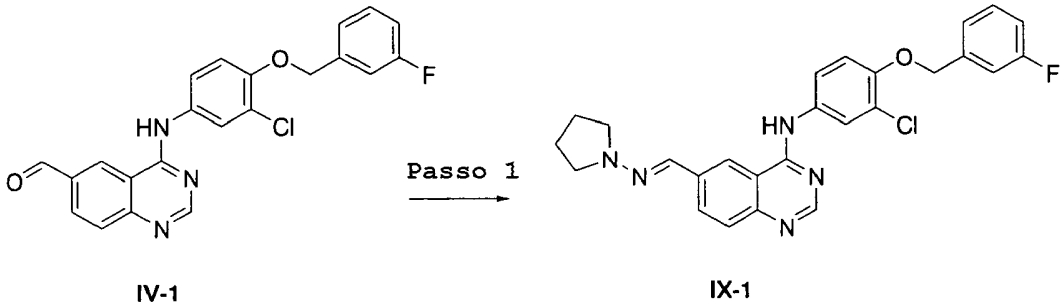
Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-222		10,18(1H, s l), 8,77(1H, s), 8,60(1H, s), 8,19(1H, dd, J = 2,0, 11,6 Hz), 7,95(1H, d, J = 3,2 Hz), 7,80(1H, d, J = 11,6 Hz), 7,67(1H, dd, J = 3,2, 11,6 Hz), 7,51-7,44(1H, m), 7,35-7,26(3H, m),7,22-7,15(1H, m), 5,27(2H, s), 4,83(2H, s), 2,27(3H, s).
VIII-223		10,12(1H, sl), 8,76(1H, d, J = 1,5 Hz), 8,59(1H, s), 8,20(1H, dd, J = 1,8 Hz, J = 8,7 Hz), 7,96(1H, d, J = 2,4 Hz), 7,81(1H, d, J = 8,7 Hz), 7,68(1H, dd, J = 2,7 Hz, J = 9,0 Hz), 7,52-7,44(1H, m), 7,35-7,16(6H, m), 5,27(2H, s), 4,65(2H, s), 2,28(3H, s).
VIII-224		10,10(1H, s), 8,59(1H, s), 8,19(1H, dd, J = 2,4, 11,6 Hz), 7,95(1H, d, J = 3,2 Hz), 7,80(1H, d, J = 11,6), 7,76-7,73(1H, m), 7,68(1H, dd, J = 3,6, 12 Hz), 7,48-7,44(1H, m),7,35-7,26(3H, m), 7,21-7,15(1H, m), 5,27(2H, s), 4,73(1H, t, J = 7,2 Hz), 4,70(2H, s), 3,44(2H, dd, J = 8,0, 15,6 Hz), 3,21(2H, dd, J = 8,0, 15,6 Hz), 2,28(3H, s)

(continuação)

Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
VIII-225		10,10(1H, s), 8,76(1H, s), 8,59(1H, s), 8,19(1H, d, J = 12,0 Hz), 8,08(1H, s l), 7,95(1H, s), 7,80(1H, d, J = 11,6 Hz), 7,69-7,66(1H, m),7,51-7,44(1H, m), 7,34-7,26(3H, m), 7,21-7,16(1H, s), 5,27(2H, s), 4,71(2H, s), 3,60-3,53(1H, m), 2,99(3H, s), 2,28(3H, s).
VIII-226		10,12(1H, s), 8,77(1H, s), 8,59(1H, s), 8,19(1H, dd, J = 2,0, 12,0 Hz), 8,08(1H, s l), 7,95(1H, d, J = 3,2 Hz), 7,80(1H, d, J = 11,6 Hz), 7,70-7,62(2H, m),7,51-7,44(1H, m), 7,34-7,26(3H, m), 7,21-7,15(1H, s), 5,27(2H, s), 4,69(2H, s), 3,22(2H, dd, J = 8,4, 16,0 Hz) 2,31(1H, t, J = 8,4 Hz), 2,28(3H, s), 2,11(6H, s).

Exemplo 12

Fórmula química 88



IV-1 IX-1

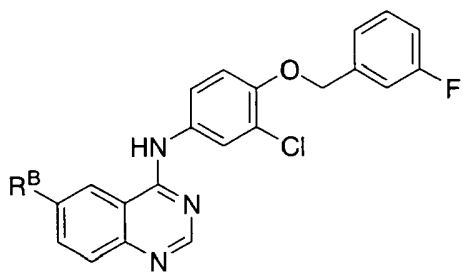
Passo 1 Síntese de 4-(3-cloro-4-(3-fluorobenziloxi)fenilamino)-6-(pirrolidin-1-iliminometil)quinazolina (IX-1)

Numa mistura de 1 mL de tetra-hidrofurano e 0,1 mL de água foram dissolvidos 40 mg de 4-(3-cloro-4-(3-fluorobenziloxi)fenilamino)-6-formilquinazolina (IV-1) e 13 mg de cloridrato de 1-amino-pirrolidina, seguidos de uma reacção à temperatura ambiente de um dia para o outro. Após a reacção, foi adicionada solução aquosa saturada de bicarbonato de sódio, seguida de extracção com acetato de etilo. A camada orgânica foi desidratada passando através de Presep (marca registada) e o filtrado foi concentrado. O resíduo concentrado foi purificado por cromatografia (eluindo com hexano: acetato de etilo = 2:1 → 1:1) utilizando uma coluna amino para obter 38 mg de 4-(3-cloro-4-(3-fluorobenziloxi)fenilamino)-6-(pirrolidin-1-iliminometil)quinazolina (IX-1) como um sólido amarelo.

RMN de ^{1}H (d_6-DMSO, δ): 9,76 (1H, s), 8,52 (1H, s), 8,40 (1H, s l), 8,08 (1H, d, J = 6,6 Hz), 8,06 (1H, d, J = 1,8 Hz), 7,76 (1H, dd, J = 6,6 Hz, J = 1,8 Hz), 7,69 (1H, dd, J = 6,6 Hz), 7,50-7,45 (1H, m), 7,35-7,26 (3H, m), 7,19 (1H, t, J = 6,6 Hz), 5,26 (2H, s), 3,39 (4H, l), 1,94 (4H, l)

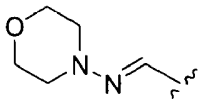
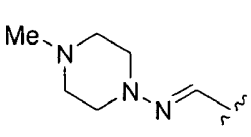
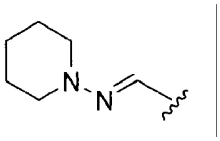
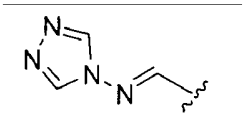
De acordo com o mesmo modo que o do Exemplo 12 foi sintetizado o composto seguinte.

Fórmula química 89

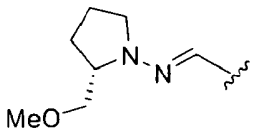
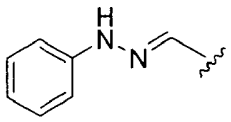
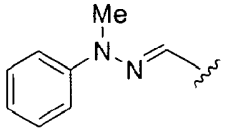
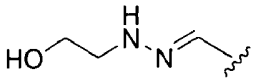


(IX)

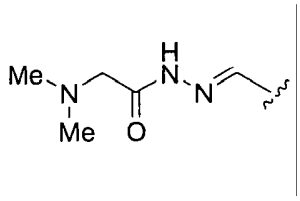
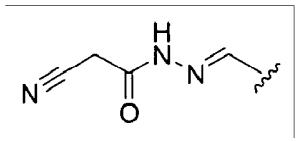
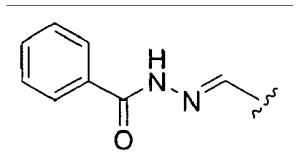
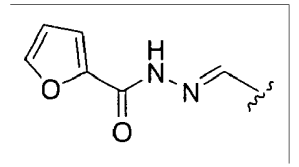
Quadro 48

Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
IX-2		9,86(1H, s), 8,56(1H, s), 8,55(1H, s l), 8,14(1H, d, J = 6,6 Hz), 8,05(1H, d, J = 1,8 Hz), 7,78-7,74(3H, m), 7,50-7,45(1H, m), 7,35-7,26(3H, m), 7,19(1H, t, J = 6,3 Hz), 5,26(2H, s), 3,18(4H, tipo t, J = 3,6 Hz), 3,20(4H, tipo t, J = 3,6 Hz)
IX-3		9,83(1H, s), 8,56(1H, s), 8,52(1H, s l), 8,13(1H, d, J = 6,6 Hz), 8,05(1H, s l), 7,77-7,73(3H, m), 7,50-7,45(1H, m), 7,35-7,26(3H, m), 7,19(1H, t, J = 6,3 Hz), 5,26(2H, s), 3,21(4H, s l), 2,53(4H, s l), 2,25(3H, s)
IX-4		9,83(1H, s), 8,54(1H, s), 8,50(1H, s l), 8,13(1H, d, J = 8,7 Hz), 8,04(1H, d, J = 2,7 Hz), 7,76-7,70(3H, m), 7,52-7,43(1H, m), 7,36-7,25(3H, m), 7,22-7,15(1H, m), 5,26(2H, s), 3,25-3,17(4H, m), 1,76-1,65(4H, m), 1,58-1,49(2H, m)
IX-5		9,19(3H, s l), 9,16(1H, s), 8,95(1H, s l), 8,52(1H, s l), 8,20(1H, d, J = 8,4 Hz), 7,95(1H, s), 7,79(1H, d, J = 6,9 Hz), 7,66- 7,60(1H, m), 7,52-7,43(1H, m), 7,36-7,14(4H, m), 5,23(2H, s)

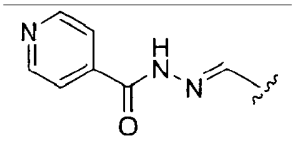
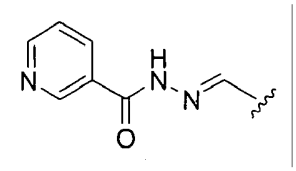
(continuação)

Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
IX-6		9,73(1H, s), 8,52(1H, s), 8,38(1H, s l), 8,13(1H, d, J = 6,6 Hz), 8,05(1H, d, J = 1,8 Hz), 7,75(1H, dd, J = 6,9 Hz, J = 1,8 Hz), 7,70(1H, dd, J = 6,6 Hz, J = 1,8 Hz), 7,50-7,45(1H, m), 7,33-7,26(3H, m), 7,18(1H, t, J = 6,6 Hz), 5,26(2H, s), 3,72(1H, s l), 3,64(1H, dd, J = 6,9 Hz, J = 2,7 Hz), 3,46(2H, dd, J = 7,2 Hz, J = 5,1 Hz), 3,13(1H, l), 1,99(3H, l,), 1,80(1H, l)
IX-7		lO,59(1H, s), 9,84(1H, s), 8,56(1H, s), 8,53(1H, s l), 8,29(1H, d, J = 6,9 Hz), 8,03(2H, s l), 7,78-7,73(2H, m), 7,51- 7,45(1H, m), 7,35-7,16(8H, m), 6,79(1H, t, J = 5,4 Hz), 5,2 7(2H, s)
IX-8		9,86(1H, s), 8,61(1H, s), 8,57(1H, s l), 8,32(1H, d, J = 7,2 Hz), 8,05(2H, J = 2,1 Hz), 7,80-7,73(3H, m), 7,52-7,45(3H, m), 7,3 7-7,28(5H, m), 7,19(1H, t, J = 6,3 Hz), 6,94(1H; t, J = 5,4 Hz), 5,27(2H, s), 3,51(3H; s)
IX-9		9,77(1H, s), 8,53(1H, s), 8,39(1H, s l), 8,09(1H, d, J = 6,3 Hz), 8,04(1H, s), 7,75-7,69(3H, m), 7,55-7,45(2H, m), 7,34-7,26(3H, m), 7,18(1H, t, J = 6,3 Hz), 5,21(2H, s), 4,69(1H, t, J = 3,6 Hz), 3,61 (2H, dd, J = 8,4 Hz, J = 4,5 Hz), 3,29(2H, m)

Quadro 49

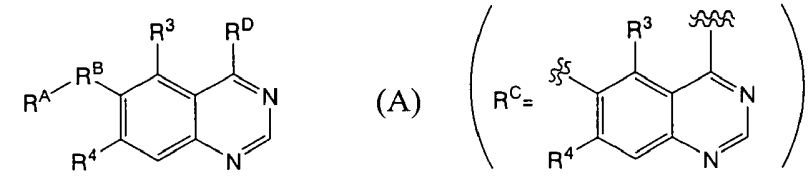
Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
IX-10		(mistura E/Z) 11,51(1H, s, menor), 11,45(1H, s, maior), 10,00(1H, s, maior), 9,89(1H, s, menor), 8,65(1H, s l, menor), 8,60(1H, s l), 8,53(1H, s l, maior), 8,26(1H, d, J = 6,6 Hz, menor), 8,22(1H, d, J = 6,6 Hz, maior), 8,04(1H, s l, menor), 8,00(1H, d, J = 1,8 Hz, maior), 7,80(1H, d, J = 6,6 Hz), 7,73(1H, d, J = 6,6 Hz), 7,51-7,45(1H, m), 7,35-7,27(3H, m), 7,19(1H, t, J = 6,6 Hz), 5,27(2H, s), 3,58(2H, s, menor), 3,08(2H, s, maior), 2,34(3H, s, menor), 2,28(3H, s, maior)
IX-11		12,04(1H, s), 9,88(1H, s), 8,64(1H, s l), 8,61(1H, s), 8,31(1H, d, J = 6,3 Hz), 8,17(1H, s), 8,01(1H, d, J = 2,1 Hz), 7,80(1H, d, J = 6,6 Hz), 7,72(1H, d, J = 6,6 Hz), 7,50-7,45(1H, m), 7,35-7,28(3H, m), 7,19(1H, t, J = 5,4 Hz), 5,27(2H, s), 4,31(2H, s)
IX-12		12,02(1H, s), 10,00(1H, s), 8,70(1H, s l), 8,65(1H, s l), 8,61(1H, s), 8,31(1H, d, J = 6,0 Hz), 8,02(1H, d, J = 1,8 Hz), 7,96-7,94(2H, m), 7,84(1H, d, J = 6,0 Hz), 7,72(1H, d, J = 13,8 Hz), 7,65-7,55(3H, m), 7,51-7,45(1H, m), 7,35-7,28(3H, m), 7,19(1H, t, J = 6,3 Hz), 5,27(2H, s)
IX-13		12,04(1H, s), 10,01(1H, s), 8,68(1H, s l), 8,65(1H, s l), 8,61(1H, s), 8,28(1H, d, J = 6,9 Hz), 8,02(1H, d, J = 1,8 Hz), 7,99(1H, s), 7,83(1H, d, J = 6,6 Hz), 7,74(1H, dd, J = 6,6 Hz, J = 1,8 Hz), 7,51-7,45(1H, m), 7,35-7,28(4H, m), 7,19(1H, t, J = 6,3 Hz), 6,74(1H, s l), 5,27(2H, s)

(continuação)

Nº do Composto	R^B	RMN de ^1H (d_6-DMSO)
IX-14		12,22(1H, s), 10,02(1H, s), 8,82(2H, m), 8,73(1H, s l), 8,65(1H, s), 8,62(1H, s), 8,31(1H, d, J = 7,2 Hz), 8,01(1H, d, J = 1,8 Hz), 7,86-7,84(2H, m), 7,73-7,72(2H, m), 7,51-7,45(1H, m), 7,35-7,28(3H, m), 7,19(1H, t, J = 6,9 Hz), 5,27(2H, s)
IX-15		12,18(1H, s), 10,01(1H, s), 9,11(1H, s), 8,80(1H, d, J = 3,3 Hz), 8,72(1H, s l), 8,64-8,62(2H, m), 8,32-8,28(2H, m), 8,02(1H, d, J = 1,8 Hz), 7,85(1H, d, J = 6,3 Hz), 7,73(1H, dd, J = 6,6 Hz, J = 1,8 Hz), 7,62-7,59(1H, m), 7,51-7,45(1H, m), 7,35-7,28(3H, m), 7,19(1H, t, J = 6,9 Hz), 5,27(2H, s)

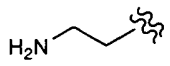
De acordo com o mesmo modo que o do Exemplo acima pode ser sintetizado o composto seguinte. Isto é, no composto representado pela fórmula seguinte geral (A):

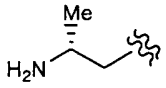
Fórmula química 90

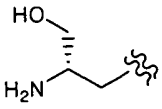


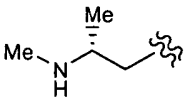
podem ser sintetizados os compostos seguintes representados por uma associação de um grupo nos quais R^A é um grupo seleccionado dos a1 a a90 que se seguem:

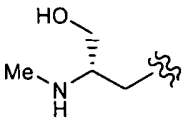
Fórmula química 91

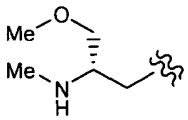
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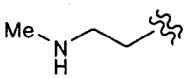
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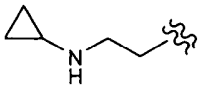
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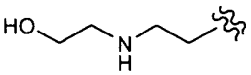
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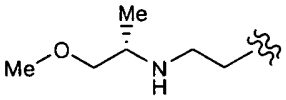
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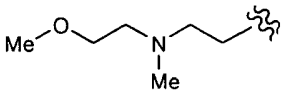
a6 

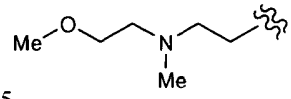
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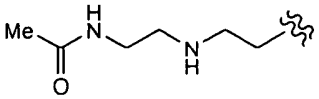
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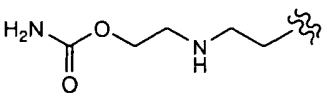
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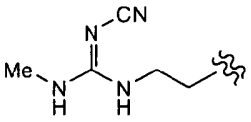
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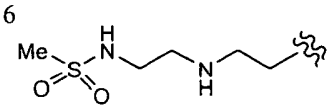
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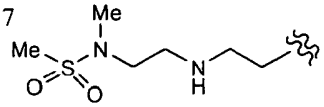
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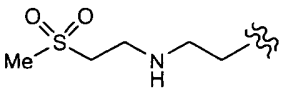
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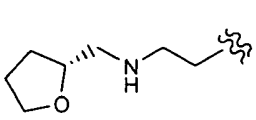
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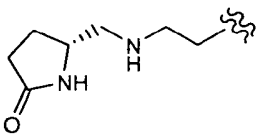
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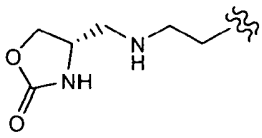
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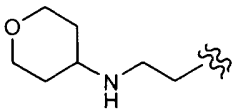
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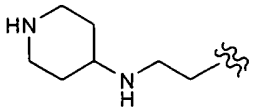
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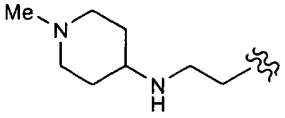
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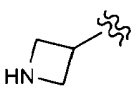
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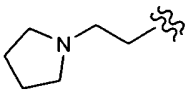
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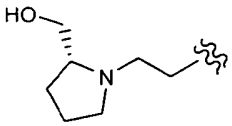
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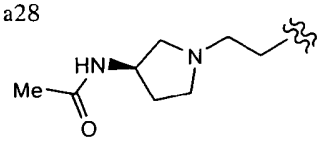
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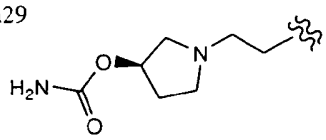
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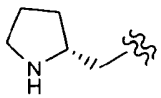
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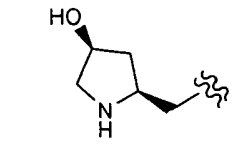
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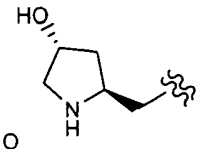
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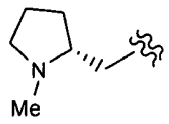
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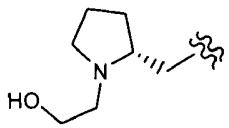
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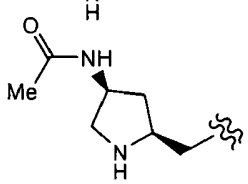
Fórmula química 92

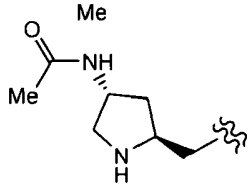
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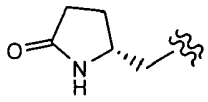
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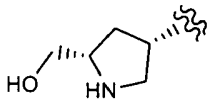
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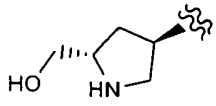
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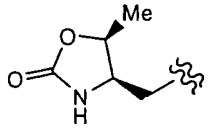
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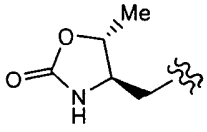
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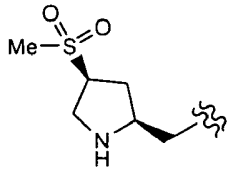
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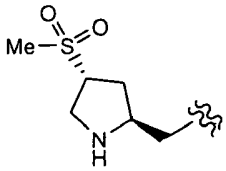
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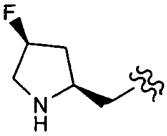
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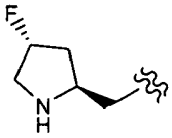
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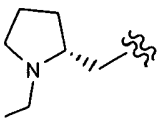
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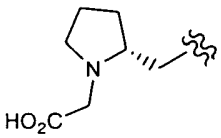
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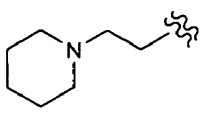
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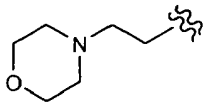
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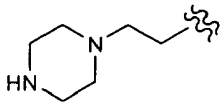
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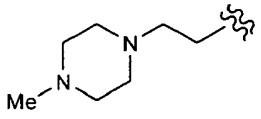
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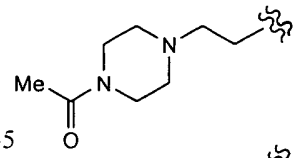
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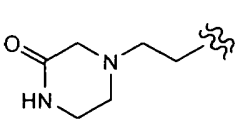
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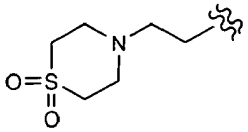
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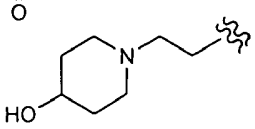
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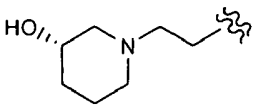
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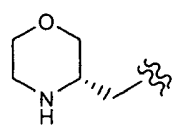
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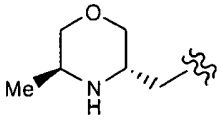
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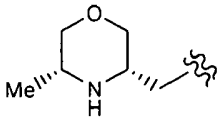
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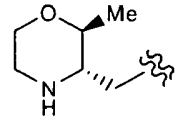
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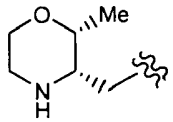
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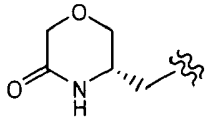
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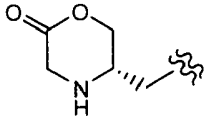
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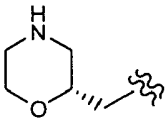
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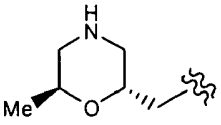
Fórmula química 93

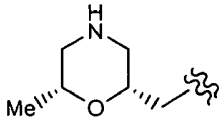
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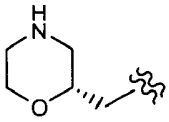
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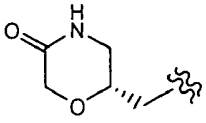
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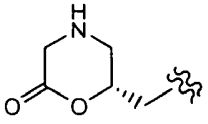
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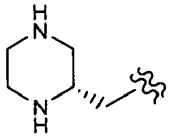
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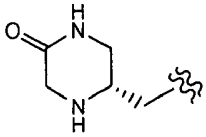
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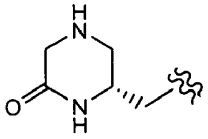
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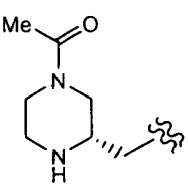
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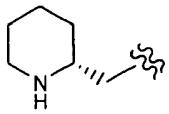
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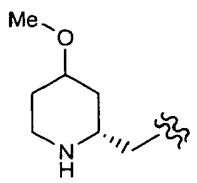
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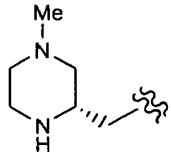
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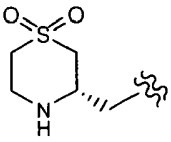
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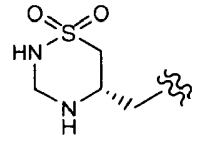
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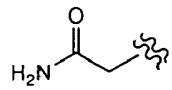
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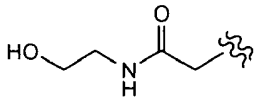
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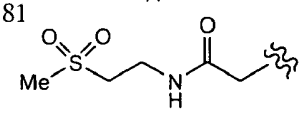
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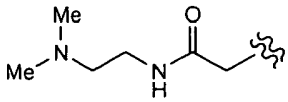
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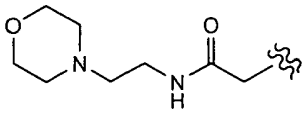
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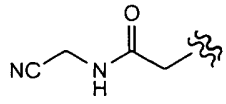
a79 

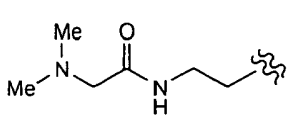
a80 

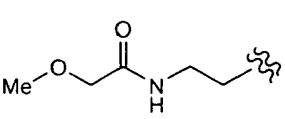
a81 

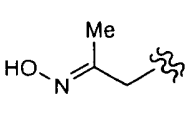
a82 

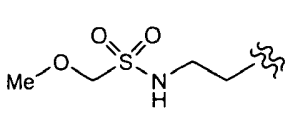
a83 

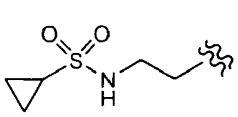
a84 

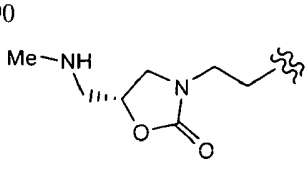
a85 

a86 

a87 

a88 

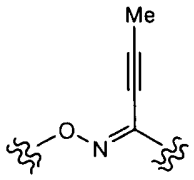
a89 

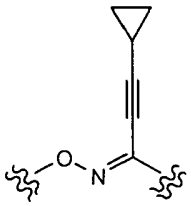
a90 

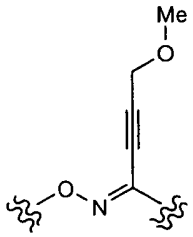
(em que Me é metilo),

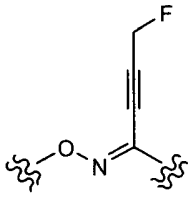
um grupo no qual R^B é seleccionado dos b1 a b6 que se seguem:

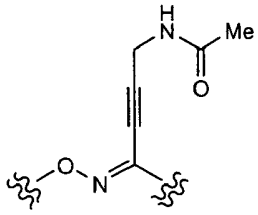
Fórmula química 94

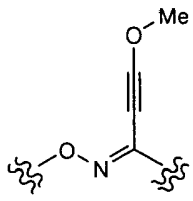
b1 

b2 

b3 

b4 

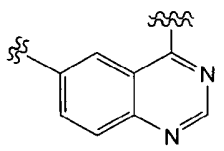
b5 

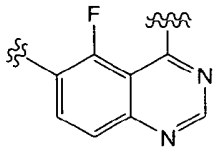
b6 

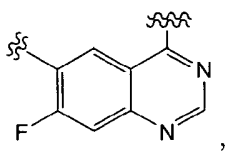
(em que Me é metilo),

um grupo no qual R^C é seleccionado dos c1 a c3 que se seguem

Fórmula química 95

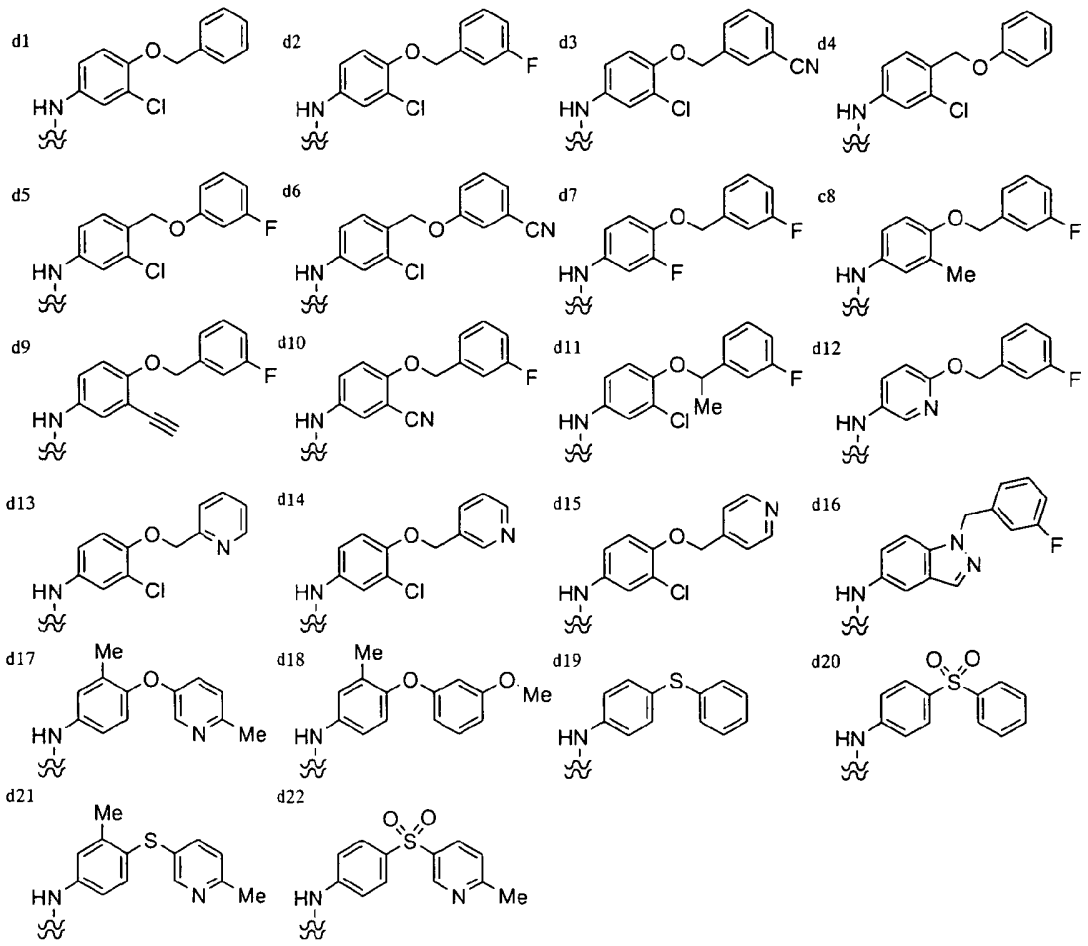
c1 

c2 

c3  ,

um grupo no qual R^D é seleccionado dos d1 a d22 que se seguem:

Fórmula química 96



(em que Me é metilo).

(a1, b1, c1, d1), (a1, b1, c1, d2), (a1, b1, c1, d3), (a1, b1, c1, d4), (a1, b1, c1, d5), (a1, b1, c1, d6), (a1, b1, c1, d7), (a1, b1, c1, d8), (a1, b1, c1, d9), (a1, b1, c1, d10), (a1, b1, c1, d11), (a1, b1, c1, d12), (a1, b1, c1 d13), (a1, b1, c1, d14), (a1, b1, c1, d15), (a1, b1, c1, d16), (a1, b1, c1, d17), (a1, b1, c1, d18), (a1, b1, c1, d19), (a1, b1, c1, d20), (a1, b1, c1, d21), (a1, b1, c1, d22), (a1, b1, c2, d1), (a1, b1, c2, d2), (a1, b1, c2, d3), (a1, b1, c2, d4), (a1, b1, c2, d5), (a1,

b1, c2, d6), (a1, b1, c2, d7), (a1, b1, c2, d8), (a1, b1, c2, d9), (a1, b1, c2, d10), (a1, b1, c2, d11), (a1, b1, c2, d12), (a1, b1, c2, d13), (a1, b1, c2, d14), (a1, b1, c2, d15), (a1, b1, c2, d16), (a1, b1, c2, d17), (a1, b1, c2, d18), (a1, b1, c2, d19), (a1, b1, c2, d20), (a1, b1, c2, d21), (a1, b1, c2, d22), (a1, b1, c3, d1), (a1, b1, c3, d2), (a1, b1, c3, d3), (a1, b1, c3, d4), (a1, b1, c3, d5), (a1, b1, c3, d6), (a1, b1, c3, d7), (a1, b1, c3, d8), (a1, b1, c3, d9), (a1, b1, c3, d10), (a1, b1, c3, d11), (a1, b1, c3, d12), (a1, b1, c3, d13), (a1, b1, c3, d14), (a1, b1, c3, d15), (a1, b1, c3, d16), (a1, b1, c3, d17), (a1, b1, c3, d18), (a1, b1, c3, d19), (a1, b1, c3, d20), (a1, b1, c3, d21), (a1, b1, c3, d22), (a1, b2, c1, d1), (a1, b2, c1, d2), (a1, b2, c1, d3), (a1, b2, c1, d4), (a1, b2, c1, d5), (a1, b2, c1, d6), (a1, b2, c1, d7), (a1, b2, c1, d8), (a1, b2, c1, d9), (a1, b2, c1, d10), (a1, b2, c1, d11), (a1, b2, c1, d12), (a1, b2, c1, d13), (a1, b2, c1, d14), (a1, b2, c1, d15), (a1, b2, c1, d16), (a1, b2, c1, d17), (a1, b2, c1, d18), (a1, b2, c1, d19), (a1, b2, c1, d20), (a1, b2, c1, d21), (a1, b2, c1, d22), (a1, b2, c2, d1), (a1, b2, c2, d2), (a1, b2, c2, d3), (a1, b2, c2, d4), (a1, b2, c2, d5), (a1, b2, c2, d6), (a1, b2, c2, d7), (a1, b2, c2, d8), (a1, b2, c2, d9), (a1, b2, c2, d10), (a1, b2, c2, d11), (a1, b2, c2, d12), (a1, b2, c2, d13), (a1, b2, c2, d14), (a1, b2, c2, d15), (a1, b2, c2, d16), (a1, b2, c2, d17), (a1, b2, c2, d18), (a1, b2, c2, d19), (a1, b2, c2, d20), (a1, b2, c2, d21), (a1, b2, c2, d22), (a1, b2, c3, d1), (a1, b2, c3, d2), (a1, b2, c3, d3), (a1, b2, c3, d4), (a1, b2, c3, d5), (a1, b2, c3, d6), (a1, b2, c3, d7), (a1, b2, c3, d8), (a1, b2, c3, d9), (a1, b2, c3, d10), (a1, b2, c3, d11), (a1, b2, c3, d12), (a1, b2, c3, d13), (a1, b2, c3, d14), (a1, b2, c3, d15), (a1, b2, c3, d16), (a1, b2, c3, d17), (a1, b2, c3, d18), (a1, b2, c3, d19), (a1, b2, c3, d20), (a1, b2, c3, d21), (a1, b2, c3, d22), (a1, b3, c1, d1), (a1, b3, c1, d2), (a1, b3, c1, d3), (a1, b3,

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(a90, b5, c2, d20), (a90, b5, c2, d21), (a90, b5, c2, d22), (a90, b5, c3, d1), (a90, b5, c3, d2), (a90, b5, c3, d3), (a90, b5, c3, d4), (a90, b5, c3, d5), (a90, b5, c3, d6), (a90, b5, c3, d7), (a90, b5, c3, d8), (a90, b5, c3, d9), (a90, b5, c3, d10), (a90, b5, c3, d11), (a90, b5, c3, d12), (a90, b5, c3, d13), (a90, b5, c3, d14), (a90, b5, c3, d15), (a90, b5, c3, d16), (a90, b5, c3, d17), (a90, b5, c3, d18), (a90, b5, c3, d19), (a90, b5, c3, d20), (a90, b5, c3, d21), (a90, b5, c3, d22), (a90, b6, c1, d1), (a90, b6, c1, d2), (a90, b6, c1, d3), (a90, b6, c1, d4), (a90, b6, c1, d5), (a90, b6, c1, d6), (a90, b6, c1, d7), (a90, b6, c1, d8), (a90, b6, c1, d9), (a90, b6, c1, d10), (a90, b6, c1, d11), (a90, b6, c1, d12), (a90, b6, c1, d13), (a90, b6, c1, d14), (a90, b6, c1, d15), (a90, b6, c1, d16), (a90, b6, c1, d17), (a90, b6, c1, d18), (a90, b6, c1, d19), (a90, b6, c1, d20), (a90, b6, c1, d21), (a90, b6, c1, d22), (a90, b6, c2, d1), (a90, b6, c2, d2), (a90, b6, c2, d3), (a90, b6, c2, d4), (a90, b6, c2, d5), (a90, b6, c2, d6), (a90, b6, c2, d7), (a90, b6, c2, d8), (a90, b6, c2, d9), (a90, b6, c2, d10), (a90, b6, c2, d11), (a90, b6, c2, d12), (a90, b6, c2, d13), (a90, b6, c2, d14), (a90, b6, c2, d15), (a90, b6, c2, d16), (a90, b6, c2, d17), (a90, b6, c2, d18), (a90, b6, c2, d19), (a90, b6, c2, d20), (a90, b6, c2, d21), (a90, b6, c2, d22), (a90, b6, c3, d1), (a90, b6, c3, d2), (a90, b6, c3, d3), (a90, b6, c3, d4), (a90, b6, c3, d5), (a90, b6, c3, d6), (a90, b6, c3, d7), (a90, b6, c3, d8), (a90, b6, c3, d9), (a90, b6, c3, d10), (a90, b6, c3, d11), (a90, b6, c3, d12), (a90, b6, c3, d13), (a90, b6, c3, d14), (a90, b6, c3, d15) (a90, b6, c3, d16), (a90, b6, c3, d17), (a90, b6, c3, d18), (a90, b6, c3, d19), (a90, b6, c3, d20), (a90, b6, c3, d21), (a90, b6, c3, d22)

O composto representado pela fórmula geral (A) inclui um seu isómero óptico e um seu racemato.

Exemplo de Ensaio 1 Actividade inibidora enzimática do composto de ensaio sobre EGFR e HER2

EGFR e HER2 purificados de um sistema de expressão em célula de insecto e um substrato biotinilado (péptido sintético de ácido glutâmico:tirosina = 4:1) foram adicionados a uma placa de 384 poços com ATP adicionado na mesma e foi realizada uma reacção enzimática à temperatura ambiente. Depois da reacção enzimática estar completa, foram adicionados um anticorpo anti-tirosina fosforilada marcado com európio e estreptavidina marcada com alficocianina e o resíduo de tirosina fosforilada foi quantificado por um método de fluorescência com resolução em tempo.

Preparação de composto de ensaio

Um composto de ensaio foi ajustado a 10 mM utilizando DMSO.

Além disso, utilizando uma solução de DMSO a 10%, foi preparada uma solução 1 mM e esta foi considerada como um ponto de concentração máxima.

Como uma série de diluição foi preparada uma série de diluição de 4 vezes até à 10ª fase.

Preparação do reagente

Preparação de tampão:

Como tampão foi utilizado TBS contendo $MgCl_2$ 10 mM, $MnCl_2$ 5 mM, Na_3VO_4 0,2 mM e 0,1% de BSA.

Enzima:

Como enzimas EGFR e HER2, as purificadas de um sistema de expressão em célula de insecto foram adquiridas de Carna Biosciences, Inc.

A solução da enzima EGFR foi ajustada a 250 ng/mL utilizando um tampão.

A HER2-cinase foi ajustada a 1000 ng/mL utilizando um tampão.

Solução de substrato:

Como um substrato foi utilizado poli-Glu-Tyr biotinilado (4:1, fabricado por CISbio). A concentração foi ajustada a 3,125 µg/mL utilizando o tampão acima.

Solução de ATP:

A concentração de ATP no estudo da enzima EGFR foi ajustada a 125 µM utilizando o tampão.

A concentração de ATP no estudo da enzima HER2 foi ajustada a 290 µM.

Reagente de detecção:

Para preparar um reagente de detecção foi utilizado TBS contendo EDTA 30mM, KF 0,8 M e 0,1% de BSA.

O anticorpo anti-tirosina fosforilada marcado com európio, PT-66K (CISbio) foi ajustado a 195 ng/mL e a estreptavidina marcado com alficocianina, SA-XL(CISbio) foi ajustada a 5 µg/mL.

Método de ensaio

Como uma placa de ensaio foi utilizada uma placa de 384 poços. Por cada poço foram adicionados 1,1 µL de um composto de ensaio, 4 µL de uma solução de substrato e 4 µL de uma solução de enzima, e foram adicionados 2 µL de uma solução de ATP para iniciar a reacção enzimática. A reacção enzimática foi realizada à temperatura ambiente durante 60 minutos e foram adicionados 10 µL de um reagente de detecção para completar a reacção. Uma hora depois de a reacção estar completa, foi realizada a medição da fluorescência com resolução no tempo.

Método de avaliação

Utilizando DMSO a 10% em vez de um composto de ensaio e admitindo que um sinal ao adicionar ATP é 0% de inibição (actividade enzimática 100%) e admitindo que um sinal na

ausência de ATP é 100% de inibição (actividade enzimática 0%) foi calculada a actividade inibidora ao adicionar um composto de ensaio.

A actividade inibidora (IC_{50} valor, nM) dos compostos descritos nos Exemplos sobre os EGFR e HER2 é mostrada abaixo.

Quadro 50

N° do Composto	EGFR(nM)	HER2(nM)	N° do Composto	EGFR(nM)	HER2(nM)
V-6	6,5	3,6	VIII-74	164	150
V-7	36	76	VIII-75	50	34
V-43	186	151	VIII-76	162	216
VIII-7	103	348	VIII-77	217	246
VIII-10	409	484	VIII-78	111	410
VIII-11	43	45	VIII-80	23	29
VIII-12	209	227	VIII-81	9,8	17,7
VIII-13	300	888	VIII-82	7,6	7,5
VIII-19	89	115	VIII-83	164	121
VIII-20	29	31	VIII-84	44	47
VIII-27	33	43	VIII-85	32	33
VIII-28	162	167	VIII-86	244	304
VIII-29	102	513	VIII-87	642	476
VIII-32	50	46	VIII-88	47	56
VIII-35	11	25	VIII-89	27	24
VIII-40	9,3	19,2	VIII-90	93	97
VIII-41	12	15	VIII-91	74	83
VIII-42	10	11	VIII-92	32	36
VIII-44	26	6,3	VIII-93	453	321
VIII-45	58	152	VIII-94	213	150
VIII-46	82	104	VIII-95	209	176

(continuação)

Nº do Composto	EGFR(nM)	HER2(nM)	Nº do Composto	EGFR(nM)	HER2(nM)
VIII-47	12	23	VIII-96	20	20
VIII-48	44	15	VIII-97	19	22
VIII-49	28	31	VIII-98	21	21
VIII-50	19	15	VIII-99	84	84
VIII-51	45	64	VIII-100	208	203
VIII-52	19	28	VIII-101	56	129
VIII-53	79	80	VIII-102	72	121
VIII-55	19	68	VIII-103	3,9	5,6
VIII-56	7,9	13,8	VIII-104	238	202
VIII-57	301	303	VIII-105	14	14
VIII-58	207	236	VIII-106	160	148
VIII-59	115	278	VIII-107	150	135
VIII-60	54	30	VIII-108	53	56
VIII-61	30	24	VIII-109	23	18
VIII-62	22	22	VIII-110	29	35
VIII-63	9,6	9,2	VIII-111	37	55
VIII-64	52	88	VIII-112	11	13
VIII-65	97	98	VIII-113	9,7	12
VIII-66	27	43	VIII-114	57	69
VIII-67	16	14	VIII-116	37	25
VIII-68	19	25	VIII-117	47	53
VIII-69	43	28	VIII-118	197	223
VIII-70	63	31	VIII-119	81	77
VIII-71	130	199	VIII-120	33	29
VIII-72	6,3	11	VIII-121	17	18
VIII-73	275	199	VIII-122	29	24

Quadro 51

N° do Composto	EGFR(nM)	HER2(nM)	N° do Composto	EGFR(nM)	HER2(nM)
VIII-123	24	38	VIII-174	25	28
VIII-124	40	38	VIII-176	23	26
VIII-125	118	103	VIII-177	7,3	5,8
VIII-126	101	123	VIII-178	8,1	8,2
VIII-127	37	35	VIII-179	4,6	5
VIII-128	15	17	VIII-180	7,8	6
VIII-129	7,1	6,3	VIII-181	6,2	5,9
VIII-130	8,1	5,2	VIII-182	4,7	7,3
VIII-131	5,8	4,4	VIII-183	7,1	8,3
VIII-132	14	14	VIII-184	10	7
VIII-133	8,4	7,1	VIII-185	6,8	12,5
VIII-134	7,1	7,4	VIII-186	19	26
VIII-135	7,6	8,1	VIII-187	10	9
VIII-136	21	21	VIII-188	20	30
VIII-137	13	14	VIII-189	17	27
VIII-139	5	3,8	VIII-190	8,9	11,1
VIII-140	5,5	4,3	VIII-191	17	42
VIII-141	10	7,9	VIII-192	6,2	14,2
VIII-142	5,5	4,4	VIII-193	14	15
VIII-143	3,5	3,6	VIII-194	8,6	13
VIII-145	9,4	8,9	VIII-195	45	43
VIII-146	12	10	VIII-196	11	20
VIII-147	13	13	VIII-197	9	21
VIII-148	6,1	5,8	VIII-198	3,6	4,6
VIII-149	13	14	VIII-199	6,3	5,2
VIII-150	12	11	VIII-200	9,7	9,6
VIII-151	20	19	VIII-205	17	13
VIII-152	2,4	4,3	VIII-207	21	17
VIII-153	10	11	VIII-208	28	23

Quadro 51

Nº do Composto	EGFR(nM)	HER2(nM)	Nº do Composto	EGFR(nM)	HER2(nM)
VIII-154	9,5	9	VIII-209	38	30
VIII-155	10	8	VIII-210	42	14
VIII-156	7	6,4	VIII-211	23	18
VIII-157	4,1	4	VIII-213	18	25
VIII-158	3,8	3,8	VIII-214	4,5	3,3
VIII-159	16	19	VIII-216	22	7
VIII-160	17	18	VIII-218	76	22
VIII-161	14	15	VIII-219	26	20
VIII-162	51	62	VIII-220	263	449
VIII-163	23	27	VIII-221	143	168
VIII-164	7,3	7,6	VIII-223	253	217
VIII-165	11	11	VIII-224	122	118
VIII-167	4,8	4,2	VIII-225	47	70
VIII-168	8	9	VIII-226	20	10
VIII-169	13	15	IX-1	138	203
VIII-170	5	5,6	IX-4	193	334
VIII-171	9,9	11,7	IX-6	344	326
VIII-172	14	16	IX-8	426	549
VIII-173	4,8	3,9			

Exemplo de Ensaio 2 Ensaio de inibição da proliferação celular in vitro do composto de ensaio

Como uma estirpe de célula cancerígena derivada de humano foi utilizado a BT-474. As células foram todas cultivadas numa incubadora a 37 °C, 5% de CO_2 num meio no qual 10% de soro fetal bovino (ICN) e uma solução de 50 unidades/mL de penicilina/50 µg/mL de estreptomicina (GIBCO) foram adicionados a Meio Essencial Modificado por Dulbecco (DMEM, Nacalai Tesque,

Inc). Foram aplicadas 3000 células/poço numa placa de 96 poços (Sumitomo Bakelite Co., Ltd.) e, no dia seguinte, foi adicionado um fármaco a uma concentração máxima de 3×10^{-10} a 10^{-5} M. Depois de cultivadas durante 3 dias, foi realizado o ensaio WST (sal de tetrazólio solúvel em água) e foi calculado um valor de IC_{50}.

A actividade inibidora da proliferação (valor de IC_{50}, nM) dos compostos descritos nos Exemplos sobre a BT-474 é mostrada abaixo.

Quadro 52

Nº do Composto	BT-474 (nM)	Nº do Composto	BT-474 (nM)	Nº do Composto	BT-474 (nM)
V-6	110	VIII-75	22	VIII-124	14
V-7	134	VIII-76	12	VIII-125	10
V-43	71	VIII-77	11	VIII-126	9
VIII-7	63	VIII-78	35	VIII-127	61
VIII-10	27	VIII-80	35	VIII-128	37
VIII-11	26	VIII-81	8	VIII-129	12
VIII-12	69	VIII-82	16	VIII-130	50
VIII-13	64	VIII-83	13	VIII-131	14
VIII-20	37	VIII-84	28	VIII-132	18
VIII-27	13	VIII-85	11	VIII-133	43
VIII-28	72	VIII-86	13	VIII-134	14
VIII-29	77	VIII-87	6	VIII-135	28
VIII-32	32	VIII-88	12	VIII-136	53
VIII-35	24	VIII-89	25	VIII-137	78
VIII-40	9	VIII-90	9	VIII-139	32
VIII-41	14	VIII-91	24	VIII-140	30
VIII-42	24	VIII-92	29	VIII-141	46
VIII-44	28	VIII-93	38	VIII-142	31
VIII-45	13	VIII-94	26	VIII-143	24

(continuação)

Nº do Composto	BT-474 (nM)	Nº do Composto	BT-474 (nM)	Nº do Composto	BT-474 (nM)
VIII-46	12	VIII-95	25	VIII-145	21
VIII-47	4	VIII-96	30	VIII-146	45
VIII-48	28	VIII-97	11	VIII-147	25
VIII-49	28	VIII-98	65	VIII-148	26
VIII-50	27	VIII-99	24	VIII-149	28
VIII-51	9	VIII-100	16	VIII-150	30
VIII-52	9	VIII-101	12	VIII-151	47
VIII-53	12	VIII-102	7	VIII-152	22
VIII-55	25	VIII-103	11	VIII-153	21
VIII-56	14	VIII-104	60	VIII-154	31
VIII-57	15	VIII-105	10	VIII-155	28
VIII-58	37	VIII-106	16	VIII-156	24
VIII-59	11	VIII-107	23	VIII-157	25
VIII-60	14	VIII-108	31	VIII-158	27
VIII-61	11	VIII-109	40	VIII-159	15
VIII-62	12	VIII-110	21	VIII-160	47
VIII-63	13	VIII-111	15	VIII-161	49
VIII-64	22	VIII-112	8	VIII-162	42
VIII-65	30	VIII-113	13	VIII-163	38
VIII-66	8	VIII-114	37	VIII-164	31
VIII-67	32	VIII-116	50	VIII-165	23
VIII-68	41	VIII-117	20	VIII-167	21
VIII-69	16	VIII-118	22	VIII-168	44
VIII-70	7	VIII-119	31	VIII-169	35
VIII-71	17	VIII-120	32	VIII-170	19
VIII-72	21	VIII-121	10	VIII-171	52
VIII-73	12	VIII-122	14	VIII-172	70
VIII-74	28	VIII-123	31	VIII-173	40

Quadro 53

Nº do Composto	BT-474 (nM)	Nº do Composto	BT-474 (nM)	Nº do Composto	BT-474 (nM)
VIII-174	14	VIII-190	14	VIII-209	19
VIII-176	26	VIII-191	33	VIII-210	31
VIII-177	79	VIII-192	24	VIII-211	16
VIII-178	36	VIII-193	25	VIII-213	33
VIII-179	48	VIII-194	25	VIII-214	25
VIII-180	5	VIII-195	29	VIII-216	32
VIII-181	13	VIII-196	28	VIII-218	41
VIII-182	20	VIII-197	14	VIII-219	45
VIII-183	10	VIII-198	10	VIII-220	23
VIII-184	9	VIII-199	33	VIII-221	15
VIII-185	12	VIII-200	8	VIII-223	6
VIII-186	29	VIII-205	31	VIII-224	1,2
VIII-187	24	VIII-207	68	VIII-225	7
VIII-188	40	VIII-208	27	VIII-226	5
VIII-189	25				

Exemplo de Ensaio 3 Ensaio de avaliação do antitumoral *in vivo* do composto de ensaio

Células NCI-N87 (estirpe de células do cancro do estômago humano) foram transplantadas numa almofada de gordura mamária de um ratinho glabro fêmea (BALB/cA Jcl-nu/nu, CLEA Japan, Inc) a 5×10^6 células/ratinho (dia 0). No dia 5 foram medidos um diâmetro comprido e um diâmetro curto de um tumor com um paquímetro, e os ratinhos foram divididos em grupos (N = 6) de modo que o tamanho do tumor entre grupos fosse igual. Foi administrado um composto de ensaio (20, 80 mg/kg) suspenso numa solução de metilcelulose a 0,5% (MC) por via oral a partir do

dia 5 durante 15 dias consecutivos, e o efeito antitumoral foi expresso por uma razão (T/C%) de um valor médio do tamanho do tumor entre um grupo administrado com composto (T) e um grupo de controlo (C; MC a 0,5%) no dia 20.

Os resultados da avaliação antitumoral in vivo do composto VIII-11 são mostrados no Quadro 54 e os resultados da avaliação antitumoral *in vivo* do composto VIII-66 são mostrados no Quadro 55.

Quadro 54

Tamanho médio do tumor (mm^3)	Grupo de controlo	Grupo administrado com 20 mg/kg	Grupo administrado com 80 mg/kg
dia 5	192	197	197
dia 20	655	356	193
T/C%	100%	54%	29%

Quadro 55

Tamanho médio do tumor (mm^3)	Grupo de controlo	Grupo administrado com 20 mg/kg	Grupo administrado com 80 mg/kg
dia 5	150	134	150
dia 20	483	154	17
T/C%	100%	32%	4%

Exemplos de Preparação

Exemplo de Preparação 1

É preparado um granulado contendo o seguinte ingrediente.

Ingrediente	Composto representado pela fórmula (I)	10 mg
	Lactose	700 mg
	Amido de milho	274 mg
	HPC-L	16 mg
		1000 mg

O composto representado pela fórmula (I) e lactose são feitos passar através de um peneiro de malha 60. O amido de milho é feito passar através de um peneiro de malha 120. Estes são misturados com uma máquina de mistura de tipo V. É adicionada uma solução aquosa de HPC-L (hidroxipropilcelulose de baixa viscosidade) a uma mistura em pó, e este é amassada, granulada (granulação por extrusão, diâmetro do poro 0,5 a 1 mm) e seca. O granulado seco resultante é peneirado com um peneiro vibrador (malha 12/60) para obter um granulado.

Exemplo de Preparação 2

É preparado um pó de enchimento de uma cápsula contendo os seguintes ingredientes.

Ingrediente	Composto representado pela fórmula (I)	10 mg
	Lactose	79 mg
	Amido de milho	10 mg
	Estearato de magnésio	1 mg
		100 mg

O composto representado pela fórmula (I) e a lactose são feitos passar através de um peneiro de malha 60. O amido de milho é feito passar através de um peneiro de malha 120. Estes e o estearato de magnésio são misturados com um máquina de mistura de tipo V. Uma trituração 10 de 100 mg é introduzida numa cápsula de gelatina dura nº 5.

Exemplo de Preparação 3

É preparado um granulado de enchimento de uma cápsula contendo os seguintes ingredientes.

Ingrediente	Composto representado pela fórmula (I)	15 mg
	Lactose	90 mg
	Amido de milho	42 mg
	HPC-L	3 mg
		150 mg

O composto representado pela fórmula (I) e a lactose são feitos passar através de um peneiro de malha 60. O amido de milho é feito passar através de um peneiro de malha 120. Estes são misturados, é adicionada uma solução de HPL-L a uma mistura em pó, e esta é amassada, granulada e seca. O granulado seco resultante é ajustado em tamanho, 150 mg do qual é introduzido numa cápsula de gelatina dura nº 4.

Exemplo de Preparação 4

É preparado um comprimido contendo os seguintes ingredientes.

Ingrediente	Composto representado pela fórmula (I)	10 mg
	Lactose	90 mg
	Celulose microcristalina	30 mg
	CMC-Na	15 mg
	Estearato de magnésio	5 mg
		150 mg

O composto representado pela fórmula (I), lactose, celulose microcristalina, CMC-Na (sal de sódio de carboximetilcelulose) são feitos passar através de um peneiro de malha 60 e misturados. O estearato de magnésio é misturado na mistura em pó para obter uma mistura em pó para transformação em comprimidos. A presente mistura em pó é directamente prensada para obter um comprimido de 150 mg.

Exemplo de Preparação 5

É preparada uma preparação intravenosa como se segue:

Composto representado pela fórmula (I)	100 mg
Glicérido de ácido gordo saturado	1000 mL

Uma solução dos ingredientes acima é administrada por via intravenosa ao doente a uma velocidade de 1 mL por minuto.

Aplicabilidade industrial

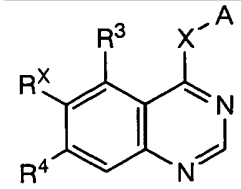
Uma vez que o presente composto tem uma excelente acção de inibição de um receptor de EGF e HER2, e é altamente seguro, este é útil como um medicamento, *inter alia*, um agente terapêutico para um cancro.

Lisboa, 15 de Outubro de 2013

REIVINDICAÇÕES

1. Composto representado pela fórmula geral (I):

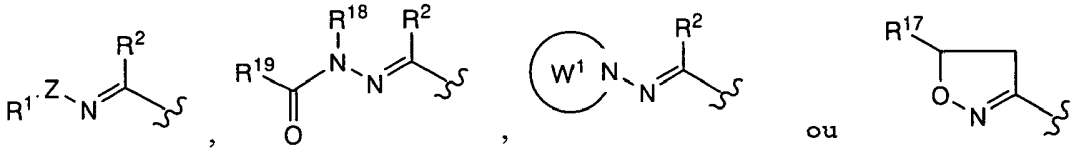
Fórmula química 1



(I)

em que R^X é um grupo representado pela fórmula:

Fórmula química 2



em que R^1 é um átomo de hidrogénio, alquilo opcionalmente substituído, alcenilo opcionalmente substituído, arilo opcionalmente substituído ou um grupo heterocíclico não aromático contendo azoto opcionalmente substituído;

Z é -O-, $-N(R^{10})-$ ou alquileno, o qual pode estar intervalado com -O- ou $-N(R^{11})-$; R^{10} e R^{11} são independentemente um átomo de hidrogénio, alquilo, acilo, alquiloxicarbonilo, alceniloxicarbonilo ou aralquiloxicarbonilo;

R^2 é um átomo de hidrogénio, alquilo opcionalmente substituído, alcenilo opcionalmente substituído, alcinilo opcionalmente substituído, cicloalquilo opcionalmente substituído, arilo opcionalmente substituído ou heteroarilo opcionalmente substituído;

R^{19} é alquilo opcionalmente substituído, arilo opcionalmente substituído, heteroarilo opcionalmente substituído ou um grupo heterocíclico não aromático opcionalmente substituído;

R^{18} é um átomo de hidrogénio, alquilo opcionalmente substituído, alcenilo opcionalmente substituído ou alcinilo opcionalmente substituído;

W^1 é um grupo heterocíclico não aromático contendo azoto opcionalmente substituído ou heteroarilo opcionalmente substituído;

R^{17} é um átomo de hidrogénio, alquilo opcionalmente substituído, alcenilo opcionalmente substituído ou um grupo heterocíclico não aromático contendo azoto opcionalmente substituído;

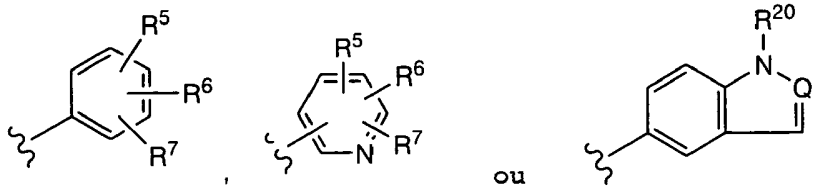
R^3 e R^4 são independentemente um átomo de hidrogénio, alquilo opcionalmente substituído, alcenilo opcionalmente substituído, alcinilo opcionalmente substituído, alquiloxilo opcionalmente substituído, alceniloxilo opcionalmente substituído, halogéneo, hidroxilo, mercapto ou amino opcionalmente substituído;

X é -O-, -S-, $-N(R^{12})-$ ou alquileno, o qual pode estar intervalado com -O-, -S- ou $-N(R^{13})-$; R^{12} e R^{13} são

independentemente um átomo de hidrogénio, alquilo, acilo, alquiloxicarbonilo, alceniloxicarbonilo ou aralquiloxicarbonilo; e

A é um grupo representado pela fórmula:

Fórmula química 3

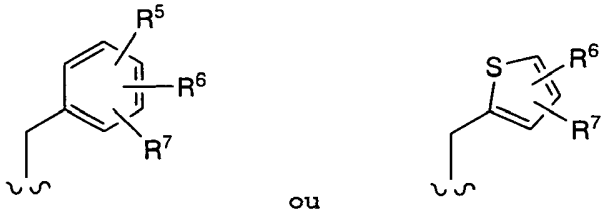


em que R^5 é um átomo de hidrogénio, halogéneo, alquiloxilo opcionalmente substituído, alceniloxilo opcionalmente substituído, alciniloxilo opcionalmente substituído ou um grupo representado pela fórmula: $-Y-R^8$ em que Y é -O-, -S-, $-SO_2-$ ou alquileno, o qual pode estar intervalado com -O-, -S- ou $-N(R^9)-$; R^8 é arilo opcionalmente substituído ou heteroarilo opcionalmente substituído; R^9 é um átomo de hidrogénio, alquilo, acilo, alquiloxicarbonilo, alceniloxicarbonilo ou aralquiloxicarbonilo;

R^6 e R^7 são independentemente um átomo de hidrogénio, alquilo opcionalmente substituído, alcenilo opcionalmente substituído, alcinilo opcionalmente substituído, alquiloxilo opcionalmente substituído, alceniloxilo opcionalmente substituído, alciniloxilo opcionalmente substituído, halogéneo, hidroxilo, mercapto, ciano ou amino opcionalmente substituído;

R^{20} é alquilo opcionalmente substituído, alcenilo opcionalmente substituído, alcinilo opcionalmente substituído ou um grupo representado pela fórmula:

Fórmula química 4



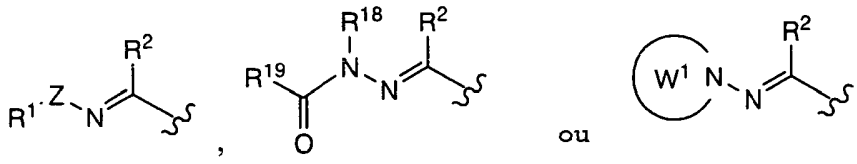
em que R^5, R^6 e R^7 são como definidos acima;

Q é N ou CH,

um seu sal farmaceuticamente aceitável ou um seu solvato.

2. Composto de acordo com a reivindicação 1, em que R^X é um grupo representado pela fórmula:

Fórmula química 5



em que R^1, R^2, R^{18}, R^{19}, Z e W^1 são como definidos na reivindicação 1,

um seu sal farmaceuticamente aceitável ou um seu solvato.

3. Composto de acordo com a reivindicação 1, em que R^1 é alquilo opcionalmente substituído com um substituinte seleccionado do grupo substituinte A consistindo de hidroxilo, heteroarilo, carboxilo, amino opcionalmente substituído, um grupo heterocíclico não aromático contendo azoto opcionalmente substituído, aminocarbonilo opcionalmente substituído e carbonilo heterocíclico não aromático contendo azoto opcionalmente substituído, ou um grupo heterocíclico não aromático contendo azoto opcionalmente substituído com um substituinte seleccionado de um grupo substituinte B consistindo de alquiloxicarbonilo, aminocarbonilo opcionalmente substituído, oxo, amino, carboxilo, ciano, cianoalquilo, hidroxialquilo, alquilcarbonilamino, alquilsulfonilamino e aminocarbonilalquilo,

um seu sal farmaceuticamente aceitável ou um seu solvato.

4. Composto de acordo com a reivindicação 1, em que R^1 é alquilo substituído com amino opcionalmente substituído com um substituinte seleccionado de um grupo substituinte C consistindo de alquilo, alcenilo, alcinilo, arilo opcionalmente substituído, aralquilo, alquiloxilo, hidroxialquilo, hidroxialquiloxialquilo, haloalquilo, aminoalquilo opcionalmente substituído com 1 ou 2 alquilo(s), alquilsulfonilo, alquilsulfonilalquilo, alquilcarbonilo opcionalmente substituído com halogéneo ou alquiloxilo, alquiloxicarbonilo, cicloalquilo opcionalmente substituído, carboxialquilo, aminocarbonilalquilo opcionalmente substituído, aminocarboniloxialquilo opcionalmente substituído, alquiloxialquilo, alquiltioalquilo, alquilcarbonilaminoalquilo,

alquilsulfonilaminoalquilo, alquilsulfonil(alquil)aminoalquilo, alquiloxicarbonilalquilo, alquiltio(hidroxi)alquilo, cicloalquilalquilo, cianoalquilo, aminoalquilcarbonilo opcionalmente substituído, heteroarilo opcionalmente substituído, heteroarilalquilo, hidroxialquiloxialquilo, um grupo heterocíclico não aromático opcionalmente substituído ou alquilo heterocíclico não aromático opcionalmente substituído, alquilo substituído com um grupo heterocíclico não aromático contendo azoto opcionalmente substituído com um substituinte seleccionado do grupo substituinte D consistindo de halogéneo; arilo; hidroxilo; oxo; aminocarbonilo opcionalmente substituído; alquiloxicarbonilo; alquilo opcionalmente substituído com um substituinte seleccionado de um grupo substituinte H consistindo de aminocarbonilo opcionalmente substituído, ciano, alquiloxilo, alquilsulfonilamino, amino, carboxilo, alquiloxicarbonilo e hidroxilo; alquilaminocarbonilo; carboxilo; ciano; alquilsulfonilo; alquilcarbonilo; alcenilcarbonilo; alquilsulfonilalquilcarbonilo; alquiloxialquilcarbonilo; alquilcarbonilamino; aminocarboniloxilo; um grupo heterocíclico não aromático contendo azoto; e carbonilo heterocíclico não aromático, ou um grupo heterocíclico não aromático contendo azoto opcionalmente substituído com um substituinte seleccionado de um grupo substituinte B,

um seu sal farmaceuticamente aceitável ou um seu solvato.

5. Composto de acordo com a reivindicação 1, em que R^{19} é alquilo opcionalmente substituído com um substituinte seleccionado do grupo substituinte A, arilo opcionalmente

substituído com um substituinte seleccionado do grupo substituinte I consistindo de alquiloxicarbonilo, aminocarbonilo opcionalmente substituído, ciano, cianoalquilo, hidroxialquilo e aminocarbonilalquilo, ou heteroarilo opcionalmente substituído com um substituinte seleccionado do grupo substituinte I,

um seu sal farmaceuticamente aceitável ou um seu solvato.

6. Composto de acordo com a reivindicação 1, em que R^{19} é alquilo substituído com amino opcionalmente substituído com um substituinte seleccionado do grupo substituinte C, ou alquilo substituído com um grupo heterocíclico não aromático contendo azoto opcionalmente substituído com um substituinte seleccionado do grupo substituinte D,

um seu sal farmaceuticamente aceitável ou um seu solvato.

7. Composto de acordo com a reivindicação 1, em que W^1 é um grupo representado por um grupo heterocíclico não aromático contendo azoto opcionalmente substituído com um substituinte seleccionado do grupo substituinte J consistindo de alquilo, cianoalquilo, hidroxialquilo, aminocarbonilalquilo, alquiloxilo, alquiloxicarbonilo, aminocarbonilo opcionalmente substituído, e ciano, ou um grupo representado por heteroarilo opcionalmente substituído com um substituinte seleccionado do grupo substituinte J,

um seu sal farmaceuticamente aceitável ou um seu solvato.

8. Composto de acordo com a reivindicação 1, em que R^2 é um átomo de hidrogénio, alquilo C1-C6 opcionalmente substituído com halogéneo, alcenilo C2-C6, alcinilo C2-C6, halogéneo ou fenilo,

um seu sal farmaceuticamente aceitável ou um seu solvato.

9. Composto de acordo com a reivindicação 1, em que um de R^3 e R^4 é um átomo de hidrogénio, e o outro é um átomo de hidrogénio, alquiloxilo opcionalmente substituído ou alceniloxilo opcionalmente substituído,

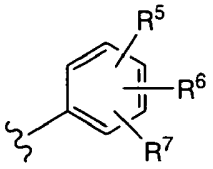
um seu sal farmaceuticamente aceitável ou um seu solvato.

10. Composto de acordo com a reivindicação 1, em que X é -NH-,

um seu sal farmaceuticamente aceitável ou um seu solvato.

11. Composto de acordo com a reivindicação 1, em que A é um grupo representado pela fórmula:

Fórmula química 6

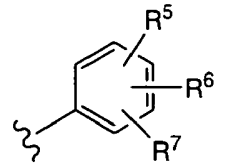


em que R^5 é um átomo de hidrogénio ou halogéneo; R^6 é halogéneo ou alcinilo; e R^7 é um átomo de hidrogénio,

um seu sal farmaceuticamente aceitável ou um seu solvato.

12. Composto de acordo com a reivindicação 1, em que A é um grupo representado pela fórmula:

Fórmula química 7



em que R^5 é alquiloxilo opcionalmente substituído com um substituinte seleccionado do grupo substituinte E consistindo de carboxilo, alcoxioxicarbonilo, cicloalquilo e aminocarbonilo opcionalmente substituído;

alceniloxilo opcionalmente substituído com um substituinte seleccionado do grupo substituinte E, ou

alciniloxilo opcionalmente substituído com um substituinte seleccionado do grupo substituinte E;

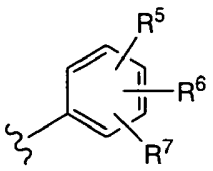
R^6 é alcinilo opcionalmente substituído, alquiloxilo opcionalmente substituído ou halogéneo; e

R^7 é um átomo de hidrogénio,

um seu sal farmaceuticamente aceitável ou um seu solvato.

13. Composto de acordo com a reivindicação 1, em que A é um grupo representado pela fórmula:

Fórmula química 8



em que R^5 é um grupo representado pela fórmula: $-Y-R^8$ em que Y é alquileno, o qual pode estar intervalado com -O-;

R^8 é fenilo opcionalmente substituído com um substituinte seleccionado do grupo substituinte F consistindo de halogéneo, carboxilo, alquilo, haloalquilo, hidroxialquilo, alquiloxilo, alquiloxicarbonilo e amino opcionalmente substituído;

piridilo opcionalmente substituído com um substituinte seleccionado do grupo substituinte F;

furilo opcionalmente substituído com um substituinte seleccionado do grupo substituinte F;

tienilo opcionalmente substituído com um substituinte seleccionado do grupo substituinte F;

tiazolilo opcionalmente substituído com um substituinte seleccionado do grupo substituinte F; ou

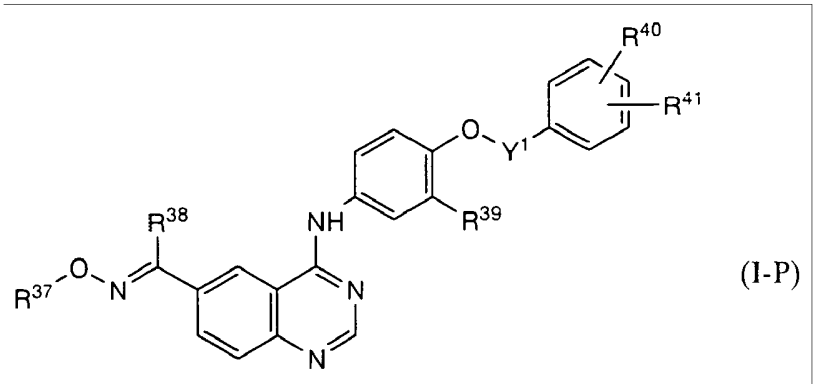
oxazolilo opcionalmente substituído com um substituinte seleccionado do grupo substituinte F;

R^6 é alcinilo opcionalmente substituído, alquiloxilo opcionalmente substituído ou halogéneo; e

R^7 é um átomo de hidrogénio,

um seu sal farmaceuticamente aceitável ou um seu solvato.

14. Composto de acordo com a reivindicação 1 representado pela fórmula (I-P):



(I-P)

em que R^{37} é alquilo C1-C10 substituído com amino ou alquilo C1-C10 substituído com amino substituído com alquilo C1-C10, hidroxialquilo C1-C10, alquil C1-C10-carbonilaminoalquilo C1-C10 ou um grupo heterocíclico não aromático; alquilo C1-C10 substituído com um grupo heterocíclico não aromático contendo azoto ou um grupo heterocíclico não aromático contendo azoto substituído com alquilo C1-C10, hidroxialquilo C1-C10 ou alquil C1-C10-carbonilamino; ou um grupo heterocíclico não aromático contendo azoto substituído com hidroxialquilo C1-C10;

R^{38} é alcinilo C2-C4;

R^{39} é halogéneo;

R^{40} é um grupo representado pela fórmula: $-Y^3-R^{42}$ em que Y^3 é alquileno C1-C4, o qual pode estar intervalado com -O-;

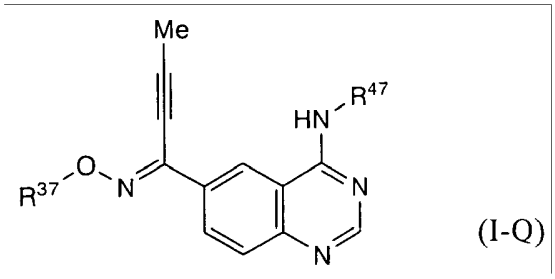
R^{42} é fenilo, fenilo substituído com halogéneo, piridilo ou piridilo substituído com halogéneo;

R^{41} é halogéneo;

Y^1 é alquileno C1-C3,

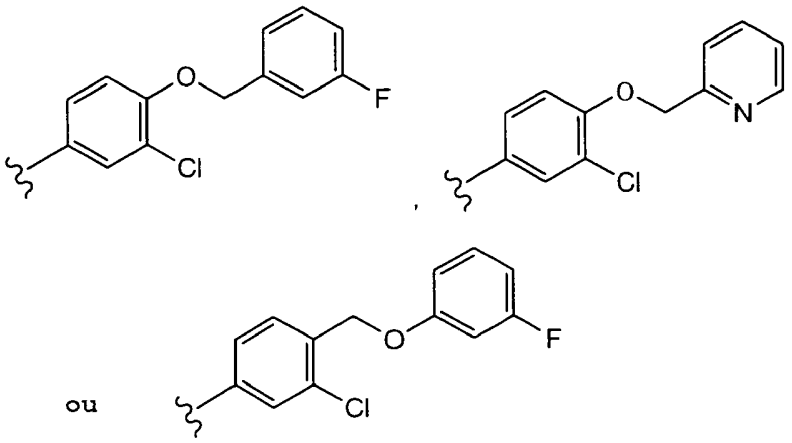
um seu sal farmaceuticamente aceitável ou um seu solvato.

15. Composto de acordo com a reivindicação 1 representado pela fórmula (I-Q):



(I-Q)

em que R^{47} é um grupo representado pela fórmula:



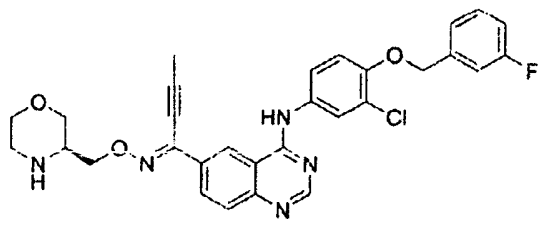
R^{37} é como definido na reivindicação 14,

um seu sal farmaceuticamente aceitável ou um seu solvato.

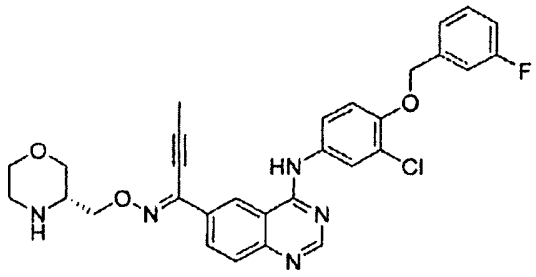
16. Composição farmacêutica contendo o composto como definido na reivindicação 1 como um ingrediente activo.

17. Composição farmacêutica útil para o tratamento de cancro contendo o composto como definido na reivindicação 1 como um ingrediente activo.

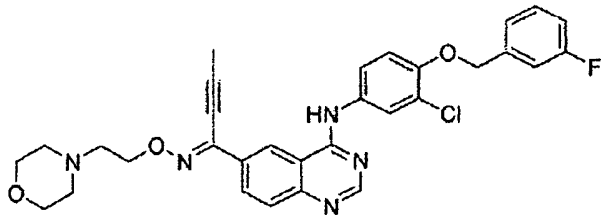
18. Composto de acordo com a reivindicação 1, o qual é representado por uma das seguintes fórmulas estruturais (1) a (7):



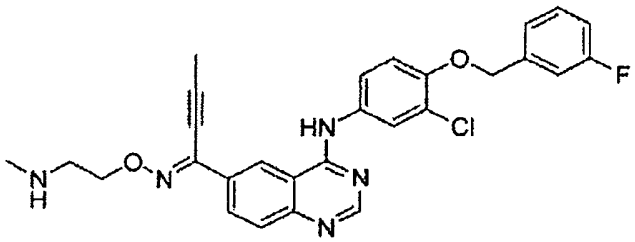
(1)



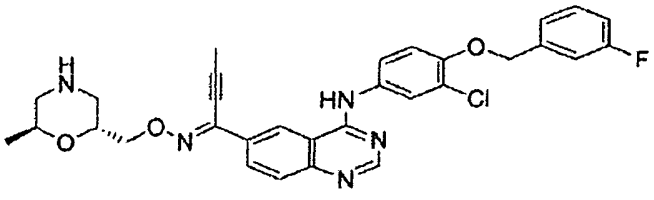
(2)



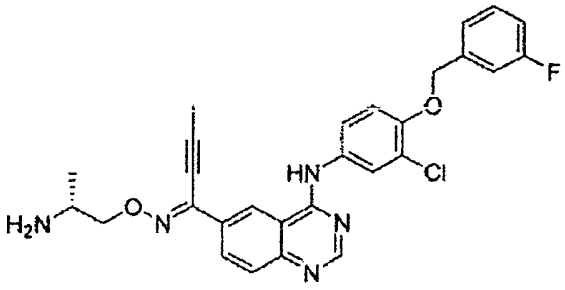
(3)



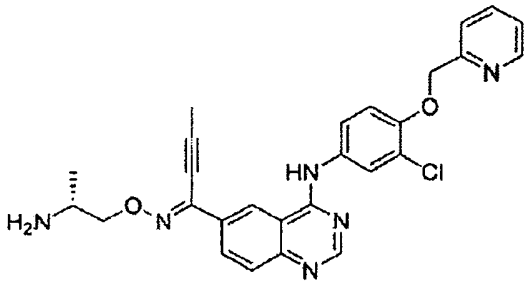
(4)



(5)



(6)



(7)

Lisboa, 15 de Outubro de 2013